

MODERN CONCEPTION OF ENCEPHALITIS LETHARGICA.

THESIS

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By

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THE MODERN CONCEPTION OF ENCEPHALITIS LETHARGICA.

It is interesting to note that it was in May 1917, when the result of the Great War was still in the balance and the most ominous part of it yet to come, when the battle of Arras and the capture of Vimy Ridge were the most recent events of interest to most people in this country, that Encephalitis Lethargica was first recognised. Professor K. von Economo published a paper on thirteen cases of a new disease which he had observed occurring in Vienna and recognised as being independent of any hitherto described. This disease was characterised by lethargy and ocular palsies, and it was owing to the striking picture produced by this former symptom that he gave it the name "Encephalitis Lethargica". His work, being carried on, as it was, at the very height of a world war, is therefore all the more praiseworthy, and his description of the disease so complete that all are agreed that it is a masterpiece. This is all the more realized when we consider how little has been added to our knowledge of the disease that was not mentioned in his original paper.

When, however, in March 1918 the disease appeared in epidemic form in England von Economo's conclusions were not accepted without reserve.

It was thoroughly investigated in England in 1918, and, with the traditional conservatism of the profession, for some time a few authorities on nervous diseases clung to the belief that it was just an unusual form of influenza or Polio-encephalitis although von Economo's paper was certainly known of in England before July 1918 in spite of the war conditions then existing.

Since May 1917, when first recognised, the disease has swept with extraordinary rapidity in epidemic form over the whole world, and has now appeared in every continent and almost every country. Wherever it has visited, whether to station itself or to pass on elsewhere, it has left death and permanent, or at any rate prolonged, incapacity in its train, as one is reluctant to admit that no curative remedy will ever be found for the numerous and persistent late manifestations so frequently observed. This alarming and rapid increase in the number of cases reported has been so phenomenal that although it is only nine years since its first appearance, there must be very few people who have not heard of it, but it may be accounted for to some extent by more frequent recognition, as, with our ever increasing knowledge of the disease, many cases of mild or unusual types which would, in its earlier days, have been missed are now correctly diagnosed

and thus add considerably to the case-incidence.

The name encephalitis lethargica with which it was originally christened by von Economo, and which has given it the popular name of "sleepy sickness", has frequently been criticized as emphasizing too much one symptom not always present. In the first place lethargy may be present in any form of encephalitis, and may be entirely absent in encephalitis lethargica, and secondly, as Wilson⁹⁴ points out, it is not the encephalitis that is lethargic but the patient who suffers from it. In other words a name derived from a clinical symptom is unscientific in the extreme. The name, of the many that have from time to time been suggested, which has found most favour as an improvement, is Epidemic Encephalitis, but, as the disease is still notifiable in England as encephalitis lethargica, it is less confusing and more respectful to its describer to continue to give it its original name.

A disease of such recent appearance and such varied character is naturally of great interest to all the medical profession, and although it is nine years since its first appearance I do not think this interest has abated to any extent, being kept up by the clinical alterations it has displayed during

that time. Having been in general practice for over two years I have had opportunities, not so easily obtainable in hospital practice, of following the whole course of a case from the beginning to the end, or up to date, in the patient's own home surroundings. I have taken it as the subject of this thesis in the hope that one more drop may be added to the pool of our knowledge of its clinical eccentricities, and it is my intention to present the modern conceptions of encephalitis lethargica illustrating them as far as possible by examples from the twelve cases I have seen. Owing to lack of laboratory facilities any original observations must necessarily be of a purely clinical nature, as general practice does not lend itself to bacteriological or pathological research.

HISTORY.

The history of encephalitis lethargica as a recognised entity dates from May 1917 when Economo's original paper appeared in the Wiener klinische Wochenschrift, recording thirteen cases he had observed in Vienna suffering from a malady manifested by lethargy and ocular palsies, to which he gave the above name. Since that time many observers have reported cases they had seen previous

to 1917 with clinical features very like encephalitis
²¹
 lethargica. Crookshank reviews the historical evidence for the occurrence of epidemics very thoroughly and traces the disease back to the time of Hippocrates whom he quotes thus: "In the winter paraplegias began and attacked many, some of whom died in a short time, for the disease was very epidemical. In other respects they were well. But in the very beginning of the Spring, Burning Fevers came on, and continued to the Equinox, and even to the Summer." He shows how during the last 450 years encephalitis has occurred in association with epidemics of cerebro-spinal fever, poliomyelitis, and influenza - grouping them all under the epidemiological heading of - epidemic encephalomyelitis. These epidemics, resembling the above diseases, were invariably put down to poisoning by either fish, sausages, ergot, or radish seeds.

Three epidemics of the past have, since the recognition of encephalitis lethargica, been thought to be identical with it. The "Schlufsucht" which occurred at Tübingen in 1712-13, and the mysterious disease "Nona" of the Spring of 1890 in Italy and Hungary were both characterized by prolonged lethargy. A full review of the latter epidemic was reported by Longuet (Hall⁴⁵) in 1892,

and the pathological sleep was then thought to be caused by the changes which were found in the grey matter of the iter and anterior part of the floor of the fourth ventricle - sleep was "localised" there. The third epidemic which has been compared to recent outbreaks is that of the electric-chorea of Dubini which occurred in Italy in 1846. In this epidemic somnolence was not a marked feature but pains and muscular twitching, such as occur from an electric shock, were the chief symptoms; lethargy followed but was considered to be due to exhaustion. Later in the epidemic the lethargy seemed more marked than could be accounted for by exhaustion and a pathological origin was suspected. This epidemic was only associated with encephalitis lethargica after 1919 when the myoclonic type of the disease first made its appearance.

Isolated cases resembling very closely the clinical picture of encephalitis lethargica have been reported by many authors as occurring previous to 1917. Thus Gayet (Hall⁴⁵) in 1875 recorded a case with marked lethargy, protracted course and exacerbations in which pathological changes were found chiefly in the mid-brain post mortem. Jelliffe recorded a case in 1890 and Bozzolo (Hall⁴⁵) one in 1900. Hall⁴⁴ saw two cases in 1903, a boy of eleven

and a woman. In a monograph by Chartier (Wilson⁹⁴) in 1907 on "acute non-suppurative encephalitis" in children from a series of eight cases mainly from the services of M. Comby of the Enfants Malades in Paris, more than one case (e.g. Case 3 a child of four months with torpor and ophthalmoplegia) may well be regarded as encephalitis lethargica. Nixon³⁰ saw a boy in 1908 in Bristol who developed the typical Parkinsonian syndrome now so frequently seen. Raymond and Claude (Hall⁴⁵) in 1909 recorded a case of "serous meningitis" manifested by fever, somnolence, and diplopia in which perivascular cuffs were found in the central nervous system post mortem, and Souques (Hall⁴⁵) records a case of paralysis agitans⁹² from a probable encephalitis in 1910. Watson saw two cases in Leeds in 1912 of what he called "focal encephalitis" which showed such symptoms as headache, vomiting, diarrhoea, pyrexia, delirium, dysphagia, aphasia, ophthalmoplegia, and temporary optic neuritis in one case. Both patients made a rapid and complete recovery, and were then decided to be a post-influenzal encephalitis. Gordon³⁸ records four fatal cases amongst children in May and June 1913 which resembled the meningitic form but differed greatly in post mortem appearances, perivascular infiltration being markedly absent in

~~in~~ the central nervous system, and acute interstitial inflammation of the salivary glands being the most striking feature. He came to the conclusion that the disease in these cases was due to an unusual action of the virus of Specific parotitis. Hall⁴⁵ records the case of a soldier invalided out of the trenches in June 1916 suffering from "atypical paralysis agitans".

A mysterious disease with an alarming mortality which occurred in epidemic form in Queensland and New South Wales in 1917 and has been described by Cleland and Campbell¹⁷, and Flexner³⁵ showed many points of similarity to encephalitis lethargica. The chief differences were the mortality of 70%, the age incidence of 50% below five years of age, it attacked males (85) more than females (36), many contact cases were observed, and the cranial nerves were not affected. They claim to have transmitted the disease to monkeys, sheep, a horse, and a calf and if this is possible it differs essentially from acute poliomyelitis. Brienl⁷ concludes that the disease was due to the same virus as acute poliomyelitis, while Cleland and Campbell believe it to be a separate entity, and call it "X disease".

On April 27th 1917, just a few weeks before Economo's paper was published, Cruchet, Moutier, and Calmette (Gullan ⁴¹) recorded forty cases of what they called "subacute encephalo-myelitis" before the Société Médicale des Hopitaux de Paris. These had been occurring around Commercy, Verdun, and later Bar-le-Duc during the winters of 1915-16 and 1916-17 and were certainly cases of encephalitis lethargica although this was not recognised until after the 1918 epidemic in France recorded by Netter ⁷⁹ which he called "l'encéphalite léthargique épidémique".

As has been indicated the evidence in favour of many of these historical cases being identical with encephalitis lethargica is extremely slender, and the differences outweigh the similarity. Diagnosis in the olden days was very different to what it is to-day, and with the lack of modern methods a definite diagnosis very often could not be made. The description of a disease written hundreds of years ago may be interpreted quite differently when read to-day, and even if these epidemics and isolated cases mentioned above were all actually encephalitis lethargica, there is no doubt that the disease was extremely rare prior to 1917, and that since that date it has rapidly become exceedingly common.

ETIOLOGY.

Our knowledge of the etiology of encephalitis lethargica is still very obscure. A great deal still remains unknown, especially from the bacteriological standpoint. From its first appearance the disease has always shown a definite tendency to occur in epidemic form, a few sporadic cases occurring in the inter-epidemic periods; this indicates that it is almost certainly due to a specific organism yet to be discovered.

Encephalitis lethargica was first recognised as such in the Winter of 1916-17 in Austria and France simultaneously and a few cases occurred also in Leipzig. It then died down, but in the first quarter of 1918 it reappeared in France and appeared for the first time in England in March and April, cases were observed also in Algiers and Berlin. Sporadic cases then occurred until September and October when it reached America and was reported in New York, Chicago, and elsewhere. During the early months of 1919 it appeared in the Netherlands, Germany, Warsaw, Italy, Sweden, and Russia, and as far afield as the Philippines and Guatemala. A small epidemic occurred in Canada in the last quarter of 1919, affecting Winnipeg, and

it became more prevalent in Italy, while a few cases were reported in India.

The most serious outbreak experienced up to that time on the continent occurred in the Winter of 1919-20, and it became established in Spain and Portugal. In France 10,000 cases are estimated to have occurred up to 1920. It also spread east, Bagdad, Palestine, Egypt, and China being invaded. During 1920, Norway, Sweden, Denmark and Finland were all appreciably affected, and in June there was an outburst in England. In January 1921 severe epidemics appeared in France and England. The Winter of 1922-23 showed recrudescences in Liverpool, and also in New York, Czecho-Slovakia, Sweden, and Poland, and it appeared in epidemic form for the first time in Scotland, especially in Glasgow where 125 out of the 189 reported cases occurred. In 1924 an outbreak was reported in Japan, and, although the epidemic as a whole showed distinct differences from encephalitis lethargica, many typical cases were encountered.

Encephalitis lethargica has appeared in Malta, and Syria, many cases have been reported from Orange River Colony and South Africa generally, also from Swaziland, Gold Coast, Australia, New Zealand

and Tasmania. It now occurs annually in Canada and the United States in the New World and it has appeared in Mexico, Brazil and Chile.

The Local Government Board made it compulsorily notifiable in England and Wales from January 1st 1919, and the statistics thus obtained show a rapid increase in the number of cases in the course of a few years. In a study of the cases which occurred in England in 1918, James⁵² found that the distribution of the disease was such that most of the cases would probably have been missed had it not been for the careful search and recent notoriety given to it. From this he concludes that some of the rare cerebral forms of poliomyelitis observed in previous years may have been cases of encephalitis lethargica. The epidemic consisted of cases scattered sporadically all over the country.

The cases notified from 1919 to 1923 for each successive year were 541, 890, 1470, 454 and 1025. In 1924, 5039 cases were notified. These figures are only reliable to a certain extent as some of the notified cases were probably wrongly diagnosed and increasing vigilance and greater experience of the disease help to swell the numbers.

At the same time many mild cases never require medical treatment, as is shown by the numbers that have come to light since, owing to the development of the characteristic after-effects, and by the large number of mild cases reported in association with a severe case which alone served to give the clue to the diagnosis; these mild cases occurring alone would certainly be missed.

In England the heaviest incidence of the disease in 1924 occurred in the second quarter, and the epidemic, which was the most severe that has so far occurred, first appeared in Lancashire. In Scotland I regret to say compulsory notification has only been introduced generally this year (January 1st 1926). Cases were observed from 1919, but did not occur in epidemic form until 1923 when it fell chiefly on Glasgow, and in 1924 it again became prevalent in Glasgow. It has never become epidemic in Ireland, but cases have been observed since 1919.

Since its first appearance encephalitis lethargica has shown a persistent tendency to recur in epidemic form during the first quarter of the year. The epidemic usually begins in November and December, reaches its maximum in February or March, and then rapidly declines in April and May.

This has so far been a characteristic feature of the disease, and, as James ⁵³ first pointed out in 1918, is an important point of distinction between it and acute poliomyelitis. Of the twelve cases I have seen, three commenced their illness in March, and one in each of the following months - January, February, April, May, July, August and October. In two cases the date of onset is unknown. The years in which they began were 1918, 1921, 1922, 1923, 1924 (six cases), 1925, 1926. Notable exceptions to the rule of spring incidence may be mentioned such as the epidemic in England in June 1920, and in Poland as early as August in 1924. The incidence in England in 1924 fell most on the second quarter of the year, not on the first. The explosive outbursts in institutions have, at the same time occurred, in two cases at any rate, at inter-epidemic periods. South of the Equator it occurs especially in the third and fourth quarters of the year, Stallybrass ⁸⁶ expresses the view that the seasonal incidence may be due to an increased susceptibility of the individual in the colder months.

Mode of life and occupation seem to play a very small part in the liability to infection. Thus in a report of 1070 cases Parsons ⁷⁸ found 734 had indoor occupations while only 133 were engaged in

work which was carried on mostly out of doors, while the remainder were of an intermediate nature. From this it would seem as if the disease attacked more especially those who spend most of their time at work which keeps them constantly indoors, but as the majority of the population fall into this group it is not of much significance. Cases have occurred in almost every occupation.

In every epidemic that has occurred it has been observed that the sexes were equally affected. Of the 1070 cases mentioned above, 639 were females and 634 males. Wherever there has been a marked difference, however, the preponderance has usually been on the male side rather than the female. Of 127 cases reported on by Crookshank¹⁹ 77 were males and 50 females, and James⁵³ 126 cases showed 68 males and 58 females.

Encephalitis lethargica has been observed to occur at all ages from the earliest infancy to extreme old age. It has developed within a very few days after birth and has occurred in patients over eighty. The main incidence of the disease, however, falls upon those approaching adult life, 25% of cases being between the ages of ten and twenty; it therefore differs markedly in this respect from acute poliomyelitis. The youngest patient in

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 Parsons' series was two weeks old and twelve were
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 under one year. James found that in the 1918
 epidemic the percentage of cases at various age
 periods corresponded very closely to the percentage
 of the total population that was living at the same
 age periods, so that the reason for the highest
 incidence being between ten and twenty may be that
 there are more people living at that period of life
 than at others.

The disease appears to affect every kind
 of race and the only observations of note on this
 point have been the high case incidence amongst the
 Jewish population in Warsaw, and the exceptionally
 high mortality when the disease attacked the natives
 of the Transvaal.

The case mortality is fairly high, but the
 figures for various epidemics and from different
 countries vary considerably. Of Economo's thirteen
 cases two died (15.5%), in England and Wales in 1918
 the case mortality was 22%, and during the 1919-23
 period 54%. Individual observers abroad have
 reported various figures such as America 7.4%, France
 40-50%, Canada (Boyd) 38%, and Russia (1919-20) 17.3 -
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 - 35%. Of other individual observers McClure
 5
 reports a case mortality of 53% and Bramwell 15.7%.

The average works out at about 27% and the extreme variability of reports is due in part to mild cases being excluded by some and included by others. The increase observed in England and Wales was also observed in New York City where in 1919 the case mortality was 26% and in 1920 37%, and in Liverpool where the figures for the 1920-1923 period were 12, 22.5, 40, and 39%. This increase in each case corresponds to an increased case incidence and the appearance of what is recognised as a more severe type of the disease. ⁷⁸ Parsons found that the case mortality was high in the first five years of life, lowest between ten and fifteen years, and then rose with each decade until in the seventh it was eighty percent. Thus the highest case incidence occurs at the age when the case mortality is lowest which is a pleasing aspect of the disease.

Evidence of contagion has only very rarely been observed and in a large number of epidemics involving hundreds of patients there has been no evidence of case to case infection at all. The cases that have occurred in this practice have been scattered all over the town and each one is practically a quarter of a mile away from any other. Although this is the general rule, exceptions have been

reported from time to time, and these have now accumulated considerably, but the very fact that every case of contact infection is considered worthy of being recorded shows their extreme rarity. Amongst the earliest demonstrations of what can happen in this direction is the Derby outbreak in a home for girls in August 1919, reported on by MacNalty in the Annual Report of the Ministry of Health 1919-20. Of twenty-one inmates twelve were affected and five died, one after only three days illness, the longest fatal case being forty-nine days. The three members of the Staff were mildly affected, and only one of them stayed in bed for a day. Their ages were 55, 34, and 30, and they suffered from vomiting and diarrhoea, faint turns, stiff-neck, and bilateral ptosis in one case. They all complained of prostration for a few days after. The other nine cases were amongst the girls aged fifteen to twenty-two, and were manifest with sore throat, drowsiness, bilateral ptosis, Kernig's sign, and lethargy as the main symptoms, although slight initial pyrexia, vomiting, vertigo, dilated pupils with sluggish reactions, paralysis of the larynx, exaggerated reflexes, rigidity of the legs, tremors and irregular jerkings of the limbs, monotonous

nasal slurring speech, and expressionless face were also observed in some of the cases. There was no other case of encephalitis lethargica or poliomyelitis in the district at the time. Ten of the cases occurred between August 14th and 17th inclusive, and the other two on the 19th and 27th respectively. This outbreak was proved to be encephalitis lethargica by the post mortem findings and by the experiments on animals which will be discussed in the section on pathology.

A second outbreak in a girls' home was reported by Krause (Hall ⁴⁵) in July 1922. Ten sleeping in the same room suffered from dysphagia, dyspnoea, diplopia, and paralysis of accommodation; nine died in two and a half days. Thirteen others were affected a few days later of which four died. The medical attendant developed symptoms eight days later, food poisoning was positively excluded.

³⁶ Fyfe reported a third small outbreak affecting four girls in the school at Radway, a remote village in Warwickshire, which occurred in September 1922. They suffered from somnolence and frontal headache, deterioration in hand-writing, and their work in school generally, and there was diplopia in one case. Emotional after-effects were observed, such as fits of laughing and crying. There was tremor with

~~with~~ spasticity and exaggerated reflexes of the legs in one, and of the right side in another when seen in February 1923. Case 1. was on holiday in Birmingham from August 7th to September 8th. Radway is four miles from the nearest railway station, and twelve miles from the nearest town, Stratford-on-Avon. Case 1. started on September 15th and the others on October 9th, 11th and 13th; all were girls between nine and thirteen years old. Ventilation and lighting were excellent. Definite case to case infection was evident as Cases 1, 2 and 3 sat close together and Case 4 not far away from Case 3. In the Summer of 1922 an epidemic occurred in an asylum in Mulheim (Stallybrass ⁸⁶), there were twenty-eight cases with thirteen deaths in two days, six being nurses and two doctors.

Numerous cases have been recorded where a mother suffering from encephalitis lethargica has infected her baby after birth, and there is positive proof that infection can occur by placental transmission. In one case myoclonus was present in the child during parturition. Typical lesions of encephalitis lethargica have been found in a four months foetus from a human case fatal during pregnancy, and experimentally the virus from a human case has been transmitted through a pregnant rabbit

to the central nervous system of the foetus in utero and produced typical lesions. Halle (Hall⁴⁴) reports the case of a four months breast-fed baby which developed the disease nine days after its mother and died five days later. In this case the possibility of the infection occurring through the milk was suggested. Another baby born healthy became weaker and somnolent, but when weaned it rapidly regained its normal health; this illness was considered to be due to toxins in the mother's milk. Harris, Pirie, Montgomery, and Legge⁷⁸ have reported cases of healthy children being infected soon after birth by the mother, and these are considered to be due to direct contact infection rather than placental transmission.

Case to case infection has also been observed in households where more than one member has been attacked. Buzzard and Greenfield¹² saw mother and son affected within seventeen days of each other, Gullan⁴¹ saw three cases in one house - the daughter, her mother, and her grandmother, also a school-boy and his mother in another house, and a man and his stepson, and two women and a baby in two other houses. De Laroche (Hall⁴⁴) reported husband and wife infected within a month, Reece (Symes³⁰) nurse and encephalitis patient, Netter (Hall⁴⁵) three

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children sleeping in the same room. Stallybrass records five cases in neighbouring streets of which four were acquaintances. In 1923 an outbreak affecting four in one house occurred. Three brothers went to a school treat on June 24th and developed symptoms respectively on July 5th, 9th and 12th. Their sister, who was not at the treat, and was last in contact with her brothers on July 18th was attacked on July 30th. They all suffered from ocular symptoms and showed changes in handwriting, there were no deaths.

There is no doubt that infectivity may persist for long periods, usually lighting up with a recrudescence of the disease. Netter (Hall ⁴⁵) saw a child of nine years who developed the disease in December 1920 while in contact with a severe case of eight months' duration with a recrudescence in November 1920. Lemierre (Hall ⁴⁵) records an attack in a man of 62 in December 1920 while attending to his daughter who commenced her illness in February 1918 and had a recrudescence in September 1920, three months before the father was affected. Hall ⁴⁵ reports the case of a woman of twenty-three who began in October 1919, and had a recrudescence in June 1922; soon after this her father had a slight

attack. Experimentally the virus can be kept alive for many months, and a positive result has been obtained in a rabbit from a case fatal after an illness lasting four years, and from the cerebro-spinal fluid of a Parkinsonian of eighteen months' duration. From the limited number of cases in which it could be calculated, it is suggested that the incubation period is probably variable like that of polio⁷⁸myelitis. Parsons places it between one day and two weeks or more, while two or three observers state that they found it to be about ten days.

The possibility of reinfection cannot be positively excluded. Price (MacNalty⁶⁰) records the case of a girl of twelve years with one and a half years of apparent complete recovery between the first and fatal attacks. Buzzard (MacNalty⁶⁰) saw a woman who had completely recovered from her first attack in 1920 and had a fatal attack in 1924 during an epidemic. On the other hand Nonne⁸⁰ believes that there may be a "normal" period of three or four years between the acute and chronic stages.

Like cerebro-spinal fever and acute polio-myelitis the virus probably first infects the upper respiratory passages, where it may remain and give rise to the "carrier" or pass on to attack the brain.

Netter (MacNalty⁷⁸) from histological observations considered the virus to be probably present in the salivary glands, and that the saliva was the chief source of infection, while Levaditi and Harvier⁷⁸ (MacNalty⁷⁸) consider that the chief route of infection is the naso-pharynx, and have not found the virus in the salivary glands. Gastro-intestinal infection probably occurs also when vomiting and diarrhoea are prominent initial symptoms, and intestinal ulcers and splenic enlargement have been⁶⁰ noted in some cases (MacNalty⁶⁰).

The question of the causal organism is so intimately bound up with experiments on animals that they are more advantageously considered together in the section which is devoted to pathology, animal experiments, and the bacteriological findings obtained from these.

Certain alleged predisposing causes may be mentioned such as previous injury to the brain, anaesthesia, and a more or less severe blow on the head. This last was mentioned in nine of Crookshank's¹⁹ cases. Of Parsons'⁷⁸ 1070 cases 114 are reported as having had a recent attack of influenza, and 34 mention overwork as an antecedent, but he points out that influenza was prevalent at the time, and that

the attack of influenza may have been the acute stage of the illness. A recent attack of influenza in other members of the household he also suggests may have been an abortive case. Encephalitis lethargica seems to predispose to certain secondary⁸⁶ invaders. Stallybrass noted diphtheria in two cases and scarlet fever and erysipelas each in two others. One case in this practice developed scarlet fever in October 1925 during his encephalitis lethargica which was of a chronic type.

Infection is probably always from case to case by contact with a patient who is or has been suffering from encephalitis lethargica or with a "carrier" who may have been attacked and recovered⁷⁸ or who may never have developed symptoms. Parsons gives examples of possible "carrier" infection. On an isolated farm in Moreton Hampstead the eldest son, who rarely left the farm, developed encephalitis lethargica in April 1919. His sister who worked in at least two large towns came home for short visits in December 1918 and just before her brother's illness. She returned again in poor health in January 1921 and died in February 1921 after an acute encephalitis lethargica. If the brother was a "carrier" he must

have infected her fourteen months after his illness, on the other hand she may have been a "carrier" all the time and finally succumbed. There is, with two possible exceptions, no evidence of infection being carried by fomites. A Warwickshire patient before her attack wore a blouse made by a dress-maker who had died from encephalitis lethargica, and a doctor in Paris was infected after wearing his father's clothes seven months after the latter's death from encephalitis lethargica although he had not previously been in contact with either his father or his father's clothes.⁷⁸ (Parsons).

There is some evidence that pregnancy occurring in a woman who has had or is having an attack of encephalitis lethargica tends to make the patient's condition worse and to unmask later manifestations. In early epidemics pregnant women appeared to be especially susceptible to infection, judging by the number of recorded cases, and great stress was laid on this by some writers. Achard⁴⁵ (Hall) considered pregnancy a reason for a grave prognosis, while Jorge (Parsons⁷⁸) ^{REVIEWING} ~~receiving~~ eighteen cases in the literature of various countries found a mortality of 72%, the general mortality being 20-30%.⁴⁹ Herd reported two cases. Both were primiparae, and they commenced during the 35th and 36th weeks of pregnancy. One died twenty days after delivery of a normal child, and the other made a slow recovery after being delivered of a still-born child, both cases

were of the myoclonic type. Spontaneous abortion
 very rarely occurs, Hall⁴⁵ mentions four cases where
 the mother died without abortion occurring. Parsons⁷⁸
 reviewing fifty cases found the majority occurred
 towards the end of pregnancy, during labour, or early
 in the puerperium, and this is the general rule. He
 also found that the mortality (44%) was not any greater
 than that of all women between the ages of twenty and
 forty who contracted the disease during the same time,
 so that the serious view at first taken of pregnancy
 as a complication has, by later experience, been
 proved to be rather exaggerated. Interference with
 the pregnancy as a line of treatment has often proved
 useless as it has produced beneficial results, and
 unless urgently necessary is undesirable.

The relation of encephalitis lethargica
 to other diseases has occupied the minds of many.
 When it first appeared in England Botulism was at
 once diagnosed, but when McIntosh⁷¹ failed to obtain
 the bacillus botulinus from the tissues or fluids of
 cases or from the suspected food, and found that serum
 from recovered cases did not agglutinate the bacillus
 and did not protect mice from infection, and expressed
 the opinion that the microscopic changes in the brains
 of fatal cases indicated an acute infection rather

than an intoxication, it was considered definitely settled that the disease was not botulism.

Its relation to influenza was not considered in Vienna, France or England in 1917-18 because there was no epidemic of the latter in the countries at the time. The first cases of encephalitis lethargica in Vienna preceded the pandemic of influenza, but in Winnipeg the outbreak followed the epidemic of influenza after a year's interval. In France, England, and the United States influenza and encephalitis lethargica during the 1918-1922 period were more or less coincident, while in Germany epidemics of encephalitis lethargica have only occurred shortly before, along with, or soon after outbreaks of influenza. Epidemics in the past of what is now believed to have been encephalitis lethargica certainly occurred in association with epidemics of influenza, but there their relationship seems to end. Both are epidemic diseases, and both produce a profound toxic action on the nervous system. In their report for March 1926 the Public Health Department for Glasgow states that during the epidemic of influenza then occurring in the city "in a number of cases attacks of influenza had been followed by encephalitis lethargica", so that evidently they were

there occurring in close association. On the other hand they differ enormously in contagiousness in their symptoms and especially in their residua; the virus of influenza has never been found in fatal cases of encephalitis lethargica, and in pathology the two are distinct. Comparing the brain lesions of post-influenzal encephalitis with those of encephalitis lethargica, they are found to be more haemorrhagic, and do not specially select the basal ganglia, while Pfeiffer's bacillus is often found.

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In Liverpool Stallybrass⁸⁶ found that the extensive wave of influenza during the Spring of 1922 was accompanied by no increase in encephalitis lethargica but rather the reverse. In his opinion, if there is any relation between the diseases it is inverted, encephalitis lethargica occurring mostly in times when influenza is absent. He concludes that: "Until more evidence is forthcoming the association of influenza and von Economo's disease may be regarded as fortuitous or non-existent", and this, I think, is the general opinion. In a number of cases, however, the initial symptoms are diagnosed as influenza, and it is only when residua develop that its true nature is recognised; in fact so much is this the case that when symptoms develop gradually any recent attack of "influenza" in the history is considered to be the acute stage.

Its relation to epidemic hiccough has been a question of great difficulty since the advent of the latter. This disease is characterized by severe hiccough lasting a few days and accompanied by slight pyrexia and catarrhal symptoms; occasionally the hiccough lasts as long as two weeks. It is very contagious, contacts not infrequently develop the disease, and doctors in attendance have been infected.

In February 1923 Hall ⁴⁵ saw three cases in one house, one of which lasted two weeks; there was an interval *the onsets of the first and second, and also between* of sixteen days between [^]those of the second and third. Almost all the cases have been males and it occurs mostly in adults. It first appeared in epidemic form in England in November 1919, about the time when the myoclonic type of encephalitis lethargica was first observed; cases were also reported from Europe and from Winnipeg where an epidemic of encephalitis lethargica occurred simultaneously. In the Winter of 1920-21 epidemics recurred in Europe, especially in Italy, Switzerland, and France where distinct waves of epidemic hiccough and encephalitis lethargica occurred together, and many French authorities consider epidemic hiccough a type of the latter disease. In the first quarter of 1924 epidemic hiccough was widespread. Hiccough was noted as a symptom of

of encephalitis lethargica in one of Economo's⁵⁵ fatal cases in 1917, and by Lord⁵⁵ at Colwyn Bay in a man of 41 with advanced phthisis who died from encephalitis in May 1918.⁶⁰ MacNalty⁶⁰ noted the symptom in five cases in the 1918 outbreak in England. In the influenza pandemic of 1918 hiccough was often a troublesome symptom and it was suggested, when epidemic hiccough appeared in epidemic form in 1920 that it was a form of influenza. Since 1918 hiccough has been frequently noted as a symptom of encephalitis lethargica.⁸⁴ Russell Brain⁸⁴ recently reported the case of a girl who had an oculo-lethargica mild attack of myoclonic encephalitis lethargica with hiccough, intermittent at first, then persistent for eight days and occurring 120 times per minute. The hiccough preceded the lethargy and she had had a previous attack with lethargy and delirium four and a half years before. He states: "This would seem to establish finally the relationship between epidemic hiccough and encephalitis lethargica." Several cases have been reported of epidemic hiccough being followed soon after by encephalitis lethargica.⁷⁸ Parsons⁷⁸ mentions a woman of 68 who had hiccough for six days, pyrexia on the seventh, and became somnolent and died on the eighth. At the antopsy

typical lesions of encephalitis lethargica were found in the cervical region of the spinal cord. Farrar⁷⁸ reported a small epidemic in Birmingham in December 1920 which seems to bring their relationship very close. A. who was suffering from epidemic hiccough went on December 20th to see Dr. L., who next day developed an ordinary cold and on December 22nd. developed hiccough which lasted two days, and subsequently two other patients of Dr. L. took the disease. G.P. dined with S. on December 16th and had epidemic hiccough from December 20th to December 24th. S. visited him on December 26th and on December 27th S. started with a typical attack of encephalitis lethargica. On January 6th 1921 P. (who worked at the same factory as A.) saw S. and on the same day developed epidemic hiccough. P. also saw F. daily and F. had had hiccough from December 18th to 21st. He also reports a girl aged 16 in Warwickshire who began with encephalitis lethargica when her father, in the same house, was recovering from twelve days incessant hiccough. The points in favour of the two being very closely related are their almost simultaneous appearance, both diseases occurring in one house, and the development of one from the other in one patient. MacNalty⁶⁰ believes

that there is strong reason for regarding epidemic hiccough as a mild or frustrated form of encephalitis lethargica. Against this view is the marked infectivity of epidemic hiccough, and the rarity of any evidence of contagion in encephalitis lethargica.

From their experiments also Rosenow and Jackson⁴⁴ (Hall⁴⁴) believe epidemic hiccough to be due to a non-filterable Gram-positive diplo-streptococcus. Hall⁴⁴ considers that as yet no dogmatic statement of their relationship is warranted.

When it first appeared in England and Botulism had been excluded, encephalitis lethargica was considered to be an unusual cerebral form of poliomyelitis (polio-encephalitis), and for some time this view was the subject of much discussion. Poliomyelitis is the commonest of the Heine-Medin diseases, the definition of which is: "An acute specific fever which may affect any part of the central nervous system and cause a variety of symptoms dependent on the portion affected", and from this definition encephalitis lethargica is certainly one of the group. Many authorities, notably Sir William Osler, for some time believed it to be Heine Medin's disease. Advocates of the epidemic constitution hypothesis would correlate cerebro-spinal fever,

acute poliomyelitis, and encephalitis lethargica as manifestations in the wake of influenza, and MacNalty⁶⁰

compares the relationship of encephalitis and poliomyelitis to that which subsists between typhoid and the paratyphoid fevers. He⁵⁸ also quotes Wickman's classification of poliomyelitis and notes that the types harmonise to a certain extent with those described by him of encephalitis lethargica in the same report, but suggests that the classification of poliomyelitis has been made on too wide a basis and that some of the rare cerebral forms reported may in reality have been cases of encephalitis lethargica. The most important points in which encephalitis lethargica differs from poliomyelitis are the seasonal and age incidences, the mortality, and the residua. Poliomyelitis is usually epidemic in Summer and Autumn, especially about September, while encephalitis lethargica has occurred chiefly in Spring. The highest age incidence in Poliomyelitis is among children under five while encephalitis lethargica occurs mostly at the middle periods of life. The mortality of 14.7% for poliomyelitis (England and Wales 1919) makes it a crippling rather than a killing disease, but encephalitis lethargica

may be described as both killing and crippling. But it is the residua that so markedly separate the two diseases and Hall⁴⁴ points out that while the residua of poliomyelitis are practically limited to greater or less permanence of the original paralysis, in encephalitis lethargica such paralyzes form a relatively small percentage of the many and severe residua.⁵ Writing in 1920 Bramwell had seen no cases of encephalitis lethargica with flaccid paralysis as occur in poliomyelitis; he also noted that when some years before poliomyelitis was common encephalitis lethargica was absent and that during the first three months of 1919 there was no increase of poliomyelitis in England and Wales when encephalitis lethargica was prevalent.⁷⁸ Parsons quotes a fatal case reported by Boyd of encephalitis lethargica in a patient who had suffered from a typical poliomyelitis in childhood, and as one attack of poliomyelitis is believed to confer complete immunity this case appears to prove them to be entirely different diseases.⁹⁴ Wilson points out that lethargy is largely wanting in polioencephalitis while meningeal symptoms occur in a much larger percentage of cases than in encephalitis lethargica. He observes that the insignificant and minor changes in the cerebro-spinal fluid are not

consistent with what is constantly found in polio-
 -encephalitis; that in many cases of encephalitis
 lethargica there is much less and a more patchy
 distribution of perivascular cellular infiltration,
 and that the haemorrhagic element is proportionally
 considerably more prominent pathologically speaking
 than in polioencephalitis of the usual type. He
 considers the infective agent akin to the virus of
 poliomyelitis but not identical. James⁵³ from his
 investigations of the 1918 epidemic found that in 25
 out of the 51 districts in which encephalitis
 lethargica was present, no case of poliomyelitis was
 reported. Having studied the 1918 epidemic MacNalty⁶⁰
 arrived at the conclusion that encephalitis lethargica
 was anatomically and clinically distinct from the
 cerebral form of poliomyelitis and constituted a
 clinical entity, and⁵⁸ expresses the view that even
 if the virus of poliomyelitis is eventually found to
 be the cause of encephalitis lethargica the clinical
 syndrome is one that is hitherto undescribed in
 epidemics of Heine Medin's disease.

PATHOGENESIS.

The ^{MORBID} ~~marked~~ anatomy of encephalitis lethargica has been thoroughly investigated and the lesions found have been sufficiently constant in a large number of cases to show that it has a pathology of its own which differs essentially from that found in any other disease. The post-mortem findings are as a rule negative, no macroscopic changes sufficient to account for death are present. Outside the central nervous system there are no constant changes. Those usually found are due to terminal complications.

The naked eye changes in the brain are usually slight, some congestion of the superficial vessels is usually present and McIntosh⁷¹ mentions dilatation of vessels of the pons and thalamic regions. Thickening and opacity of the meninges is occasionally present, Bassoe and Hassin (Hall⁴⁵) found the pia opaque especially around the cerebellum, and da Fano and Ingleby²² mention milkiess of the pia-arachnoid. Definite meningeal haemorrhages have been noted by Buzzard and Greenfield¹², and Bramwell and Miller⁵ found a surface haemorrhage over the cerebellum in one case. Occasionally there is some excess of cerebro-spinal fluid. On section of the brain there are signs of congestion giving the cortex a pink colour, and disseminated miliary or punctiform

haemorrhages are visible. These are seen to affect especially the grey matter and the minute haemorrhagic points or small haemorrhages give to it a mottled appearance. This is seen chiefly in the basal ganglia and the grey matter around the aqueduct of Sylvius and in the anterior part of the floor of the fourth ventricle.

On microscopic examination the most striking feature is the infiltration of the adventitial sheaths of the blood vessels with several layers of small round cells. This perivascular infiltration is the most characteristic pathological appearance of encephalitis lethargica. It affects chiefly the smallest or post-capillary veins although the larger veins, the arteries, and the capillaries may also be involved. The perivascular cellular infiltration may be of varying thickness in one or more layers and sometimes only affects part of the circumference of the vessel. The cells taking part^{are}/chiefly large and small mononuclear lymphocytes and plasma cells.

⁶²Marinesco considers that endothelial cells and ⁶³fibroblasts may be present. He also found a few polynuclear cells containing granules of melanotic

pigment and occasional eosinophils. McIntosh⁷¹
 described a certain number of polyblasts and found
 polynuclear leucocytes noticably absent, while
 Bramwell and Miller⁵ found them in considerable
 numbers in one case. Hume Nattrass and Shaw⁵¹ found
 abundant polynuclear cells in the case of a child of
 six dying on the twenty-second day. Da Fano²⁴
 found the cellular infiltration consisted of
 lymphocytes and polynuclear leucocytes and he²⁶ found
 the polynuclears predominated in a case fatal in
 thirty-six hours. Where the changes are most marked
 almost every small vessel has a smaller or larger
 "cuff" of small round cells, but Greenfield³⁹ states
 that perivascular infiltration may be absent where
 other morbid changes are present. The infiltration
 occupies chiefly the Virchow-Robin space, and the
 intima in most cases remains intact. It is always¹²
 patchy in its distribution. Buzzard and Greenfield
 believe these cells to be returning to the vessels
 and not leaving them. Dilated and engorged
 vessels seen macroscopically may simulate haemorrhages;
 such dilatation and engorgment of the vessels is
 sometimes marked.

Miller⁵ states that haemorrhage was not a
 conspicuous feature and McIntosh⁷¹ mentions "some
 small microscopic haemorrhages", but Marinesco⁶²

found numerous haemorrhagic foci circumscribed around the walls of small vessels, and red corpuscles were mingled with the cells of the inflammatory infiltration, or constituted a kind of covering and floated around the vessels. He states that in spite of the very great number of haemorrhages the vessel wall did not appear to be necrosed, but sometimes a solution of continuity of the vessel wall could be seen. Buzzard and Greenfield¹² describe as common a small or large ring of haemorrhage round a congested vessel into the perivascular space of His, tearing the glial fibres from the vessel walls and stretching them in a tangential manner. In some cases, usually around veins, the haemorrhage breaks through this ring and spreads into the tissues. The haemorrhage is always patchy and irregular only affecting one or two vessels out of many, it is most conspicuous in the cortex and the grey matter under the floor of the fourth ventricle. Buzzard and Greenfield¹² found infarction a conspicuous feature in some cases and describe a second form of haemorrhage in association with it. There is a central focus where the nervous tissue is completely necrosed and ploughed up with multiple haemorrhages. At the edges of this area are numerous petechial haemorrhages lying in the

tissues at a greater or smaller distance from the vessel from which they seem to arise. In some cases the thrombosed artery causing infarction could be seen. Haemorrhage in this case seems to be from small arterioles and under much greater pressure than the former, sudden spurts of blood rather than the slow oozing of the commoner type. They believe that in two of their cases infarction was the cause of the sudden aggravation of symptoms resulting in death. Venous thromboses is sometimes a conspicuous feature, and Buzzard and Greenfield found it to be even more constant than haemorrhage. In large or small veins thrombi in all stages of resolution were seen consisting of a fine reticulum occupying a part or the whole of the lumen, and usually containing a large number of polynuclear leucocytes and lymphocytes in its meshes.

65

Mc Alpine found calcification of the vessel walls affecting especially the anterior part of the globus pallidus, and mulberry fatty globules lying free in the supporting tissues and going on to form calcified granules, in both acute and chronic cases. The calcification may be preceded by hyaline, or occasionally fatty, degeneration of the media.

It may appear as early as the fourth day of the illness (e.g. Case 4), and age plays no part in its production. The calcification starts between the adventitia and the media, spreading into the media. Calcareous matter is deposited in the form of small granules which coalesce to form solid plaques which may entirely surround the vessel, while the lumen and intima are usually unaltered. It is found most commonly in the walls of arteries and capillaries, the veins being usually less affected. This calcification he believes to be due to bacterial toxins on the analogy of the similar changes which occur in cases of carbon monoxide poisoning.

Besides the perivascular infiltration cellular infiltration also occurs in certain areas of grey matter apart from the vessels. Foci of cells are present in the nervous tissues diffusely scattered through the parenchyma, but bearing a relation in their distribution to the adventitial infiltration, though Marinesco⁶², and Bassoe and Hassin (MacNalty⁷⁸) found that the interstitial changes might be altogether independent of vascular infiltration. This parenchymatous infiltration consists of the same types of cells as those found

in the perivascular infiltration, lymphocytes and plasma cells, and a few polynuclear leucocytes.

⁶³Marinesco described glial and stellate cells and giant cells with abundant protoplasm, one or more eccentric nuclei, and numerous processes, in the cellular foci and ⁷¹McIntosh found some of the foci to consist of proliferated glial cells. Von Weisner ⁷⁸(MacNalty) in his cases detected "nests", or small groupings of polynuclear leucocytes in isolated spots ⁵¹of the parenchyma, and Hume Nattrass and Shaw found numbers of polynuclears present in the foci of ¹²cells in one case. Buzzard and Greenfield noticed especially excess of plasma cells in the tissues in the medulla in their case 17.

Oedema of the brain substance has been ⁵described by Bramwell and Miller , and by Hume ⁵¹Nattrass and Shaw . The former of these investigators found it striking in certain situations but often ill-defined and spreading beyond the area of the brain associated with clinical symptoms. It consisted of a dilatation of the perivascular lymph spaces, and an interstitial dropsy most striking in the third nerve nucleus and in the nerve fibres in the pons. The initial stage is a bubble-like clear space which appears in the substance of the pons, separating the nerve elements from one another and

extending often in a longitudinal fashion for some distance, especially along the third nerve before it leaves the pons, splitting and separating the fibres from one another. Oedema was also found in the substantia nigra.

There is always a certain amount of toxic degeneration of the nerve cells varying greatly both in extent and degree. The changes are as a rule slighter than one would expect, and the more advanced changes are rarely met with. Loss of staining of the Nissl bodies and excess of pigment in the cells, relative perinuclear chromatolysis but not complete achromatosis, eccentric pale-staining nucleus with the nucleolus staining well, reduction in volume of the cell body and in the number of prolongations, and multiplication of the satellite neuroglia cells are the changes that have been most commonly met with. Proliferation of the glial nuclei to a greater or less extent is a constant feature.

Neuronophagia, such as occurs in poliomyelitis, is very rarely met with, but sometimes occurs. ⁷¹McIntosh found no evidence of neuronophagia but ¹²Buzzard and Greenfield describe it as perhaps the most constant change of all, and consider

the cells taking part to be of mesoblastic origin, many being closely allied to plasma cells, their cytoplasm being free from granules and the outer border rounded and clearly defined. In the most affected areas almost every nerve cell had several such cells in close relation to it, but they never saw the dense clusters of cells such as invade the anterior horn cells in poliomyelitis.

⁷¹

McIntosh did not find the ganglion cells appreciably affected but da Fano and Ingleby²² lay stress on the changes in the nerve cells, and found all degrees from slight chromatolysis to complete disappearance of the Nissl granules, atrophy of the proto-plasm, and shrinkage atrophy and final disappearance of the nucleus. They found a granular black pigment-like material in cells where pigment is not generally found, and consider these to bear some indefinite relationship to the "minute bodies" they describe. The granules were spread evenly over the cells, but varied in number and size; they were found in all sections between the thalamus and the medulla and to a less extent in the cortex and spinal ganglia. Granules were also present in the tissues outside the nerve cells and in phagocytes.

The lesions of encephalitis lethargica may be found in any part of the central nervous system, the meninges, any part of the white or grey matter of the brain or spinal cord, and even the nerve trunks or ganglia may show changes. There is, however, a tendency to attack the grey matter rather than the white, and special areas of grey matter are those chiefly affected. These are the basal ganglia and the grey matter of the mid-brain and pons Varolii, in the crura cerebri extending upwards and downwards. Especially in the dorsal region of the grey matter, the tegmental region and locus niger at the level of the crura, and round the aqueduct of Sylvius, and in the floor of the fourth ventricle in the pons. The nuclei of the cranial nerves, especially the third and sixth are, therefore, frequently involved. The changes in the medulla are usually much slighter, and the spinal cord usually shows no changes, but where jerkings of the legs and abdomino-thoracic pains have been the chief symptoms the cord has been found mainly affected. ⁶³ Marinesco found well defined lesions of the upper cervical region of the cord and in two cases profound lesions of the cells of Purkinje were observed. In the latter, no cells were absolutely normal, the Nissl bodies had disappeared from all,

the cytoplasm was pale and homogeneous, the nuclear membrane was indistinct and the nucleolus deeply stained. There were no inflammatory changes in the cerebellum, and he believes the degenerative changes in the cells were due to toxins. Buzzard¹¹ describes a series of cases with the chief incidence in the cerebral hemispheres in which haemorrhage was a conspicuous feature, and da Fano²⁶ found haemorrhages almost exclusively in the cortex in a case simulating cerebral haemorrhage. There are usually no marked changes in the meninges except an insignificant increase of cells in the pia-arachnoid especially around the vessels. Inflammatory changes in cranial nerve trunks have been observed in some cases. Marinesco⁶³ detected cellular infiltration in the roots of the vagus and hypoglossal nerves. Burrows⁹ describes three cases with inflammatory changes in the cranial nerve trunks amounting to a definite neuritis, but bearing no apparent relation to the clinical symptoms. The nerves affected were the second to the eighth inclusive. Hammes and McKinley⁴⁷ found perivascular infiltration and sub-arachnoid haemorrhage in the root of the fifth nerve in one case. Inflammatory areas have been found in the

Gasserian ganglion and also in spinal ganglia where neuralgic pains have been prominent symptoms, and Calhoun (Hall⁴⁵) has found calcified deposits in a posterior root ganglion.

Summing up the changes one may say that the lesion of encephalitis lethargica is definitely inflammatory and the essential changes consist of a small cell infiltration of the perivascular lymph sheaths and of certain areas of grey matter especially in the basal ganglia, mid-brain, and pons, with degenerative changes of the nerve cells and proliferation of neuroglia. MacNalty⁷⁸ suggests that the inflammation is a slow process. In one case fatal on the seventh day the histological findings were almost completely negative, and in a case of his own fatal within six days, there were only a few areas of round cell infiltration in the basal ganglia with marked distension of the small cerebral vessels suggesting an early stage of the disease. In four cases of the Derby outbreak fatal in from three to ten days there were completely negative findings by McIntosh and Turnbull, and da Fano and Ingleby.

¹² Buzzard and Greenfield consider vascular congestion the first change, followed by toxic degeneration of nerve cells and neuronophagia, then proliferation

of the mesoblastic cells of the vessel walls and infiltration of the nervous tissue with these, and lastly, small cell infiltration of the Virchow-Robin space and glial proliferation. They found round cell perivascular infiltration present in all cases fatal within a month or two of the onset.

Of particular interest is the finding by da Fano and Ingleby²² in 1919 of minute granules in the protoplasm of certain groups of nerve cells from fatal cases of encephalitis lethargica.²³ Da Fano later found, within and without the nerve cells, and also within and without the cells infiltrating the salivary glands in an acute case, minute forms to all appearances consisting of a central generally basophil particle and of a delicate little stainable body irregularly round or oval in shape. To these he gave the name "minute bodies" and found them to be generally discrete and provided with one granule, but dumb-bell shaped forms occurred as well as others with two central particles arranged in pairs. Da Fano²⁴ considers the central granule to be made of a substance resembling chromatin, and found that the body or halo could be stained pale green or bluish with Giemsa, one large body in the nucleus of a cell

appeared like a conglomeration of halo-bodies, another name he applies to them, and he states that the bodies he describes are very similar to the Negri bodies of rabies. In four fatal cases Hume⁵¹ Nattrass and Shaw found similar bodies confined to degenerative neurons in the basal ganglia and brain stem. Levaditi⁷⁸ Harvier and Nicolau (MacNalty) have found cell-inclusions, similar to those described by da Fano and Ingleby in 13% of cases of the disease experimentally produced in animals.²⁵ Working with the virus of herpes febrilis da Fano has found "minutes bodies" in the brains of rabbits injected with this virus, and he believes that the structures observed by Levaditi and his colleagues are identical morphologically with those he found in herpetic meningo-encephalitis.

⁹⁴
Economo's case ten (Wilson) was a girl of fourteen whose illness lasted about a month with fairly characteristic symptoms and who died on the day of admission to the clinic. Economo states that the pathological appearances were those of a polio-encephalitis, but not of a haemorrhagic type. Emulsion of the brain and cord was injected subdurally into a macacus rhesus by von Wiesner. The animal died in 46 hours with profound stupor for 24 hours and paresis of the right leg. The brain showed the

appearances of an acute haemorrhagic encephalitis and from it von Wiesner recovered Gram-positive diplo-
-treptococci, a bouillon culture of which when injected into apes produced somnolence and muscular weakness, and peritoneal injections in rabbits produced death from internal haemorrhage. (A Berkefeld filtrate of the patient's brain was injected into one monkey with a negative result.) Von Wiesner believes the organisms described above to be the cause, and he recovered them from all of Economo's
78
five fatal cases (MacNalty). He describes them as pleomorphic, isolated cocci, assuming both in culture and in the tissues the shape of elongated, oval, or short thick bacilli; they tend to degenerate in the tissues, and globoid bodies unevenly stained but retaining some of the "Gram" (whether acid or alcohol fast is not stated) were seen in abundance. In fluid cultures they readily grow in chains. They are found in sections of the leptomeninges, but are scanty and difficult to discover. They were not found in the inflammatory foci in the brain. Isolation is difficult, they grow best anaerobically and can be cultured on glucose-agar. These findings have not been confirmed by others and the prevailing opinion is that he was



dealing with a contamination. Rosenow and Jackson⁴⁵ (Hall) found undoubted cocci or diplococci in twenty-one cases, and Meyer⁷⁷ has obtained a streptococcus from the blood of a case that recovered.

⁷¹
In 1918 McIntosh reported his first experiments on animals. Brain emulsion from eight fatal cases of encephalitis lethargica were inoculated into macacus rhesus monkeys with entirely negative results. In 1920 McIntosh and Turnbull⁷² working with the brain of one of the fatal cases of the Derby outbreak succeeded in transmitting the disease to a Patas monkey. The patient, a girl of seventeen, died on the eighth day of her illness. Filtered (Berkefeld) brain emulsion was inoculated, 1 c.c. intracerebrally, and 5 c.c. intraperitoneally into a Patas monkey. Pyrexia and convulsions developed on the sixth day and a fit occurred on the fifty-eighth day. It became drowsy on the sixty-second day and died on the sixty-sixth day. At the autopsy there were no lesions outside the central nervous system, but there was active inflammation in the posterior part of the left basal ganglia and the junction of the left basal ganglia with the mid-brain, and evidence of neuronie degeneration. An emulsion of the brain of this animal was inoculated by McIntosh⁷³ into a female

macacus cynomolgus and produced the symptoms and post mortem signs of encephalitis lethargica, and he obtained a second passage from this animal to a young male baboon and to a rabbit with similar results. The disease occurred spontaneously in a male macacus cynomolgus, which he was using as a control, before any symptoms had appeared in those inoculated, with typical symptoms and pathology.

Strauss⁸⁷ Hirshfeld and Loewe in 1919 reported the results of their experiments with macacus rhesus monkeys inoculated subdurally with brain emulsions of fatal cases, and with Berkefeld filtrates of nasopharyngeal washings of cases of Encephalitis lethargica. Monkey No. 1. was inoculated subdurally with brain emulsion, next day it was ill, and the cerebro-spinal fluid contained 90 mononuclear cells per c.m.m. Two days later the post mortem showed multiple haemorrhages, a moderate meningitis, and perivascular infiltration with mononuclear cells. Monkey No. 2. was inoculated with the brain emulsion of monkey No. 1. and died of trauma. Monkey No. 3. was inoculated with the same brain emulsion with no result. Monkey No. 4. was inoculated with the filtered nasopharyngeal washings of a case of

encephalitis lethargica and developed a paresis of a leg followed by recovery. Monkey No. 5. was inoculated with similar washings and next day had right hemiparesis with paresis of the external rectus of the left eye. Three days later it had a fit ending in stupor. It was killed on the sixth day and showed the same post mortem signs as monkey No. 1. Monkey No. 6. was used as a control. Monkey No. 7. was inoculated with the brain emulsion of monkey No. 5. and developed paresis of the right arm and leg on the second day which lasted till the fifth day. The post mortem signs were as in monkey No. 1. and a large haemorrhage with necrosis at the site of the peritoneal injection. Referring to their cryptic report Mc Intosh⁷² considers that the short incubation period and the type of lesion suggest that it was not encephalitis lethargica, and certainly the symptoms in these and also in Mc Intosh's own experiments can hardly be said to be specific; they are so unlike the disease as seen in human beings that it needs considerable credulity to accept them as one and the same. In later experiments Loewe and Strauss⁴⁵ (Hall) have been able to obtain a virus from the brain and tissue fluids of cases of encephalitis

lethargica which produced positive results in rabbits and monkeys. This virus could be passed through many series and could be cultured from the experimentally produced disease and again produce it in other animals.

⁷⁸
Levaditi and Harvier (MacNalty) claim to have transmitted the disease to rabbits and obtained a specific virus. They state that the virus is pathogenic for the rabbit and guinea-pig, but only slightly for the monkey. They found that encephalitis lethargica may be transmitted to the rabbit intra-cranially, by the orbit, by injection into a peripheral nerve, or into the testicle. In December 1920 they published a series of successful experiments at the Pasteur Institute comprising long continued transmission of the virus. Their virus obtained from the brain of a fatal human case of encephalitis lethargica was kept alive month after month by repeated inoculation into rabbits, and a virus obtained from a nasopharyngeal swab from a human case gave typical positive results in rabbits. Both viruses appeared identical. The incubation period varied with the site of inoculation, on the abraded cornea it was 8 to 12 days, but intracerebrally it was 4 to 6 days, in especially susceptible animals

it was shorter. Enucleation of the eye twenty-four hours after corneal inoculation did not prevent infection. Veratti, Sala, Douglas, and Flexner have obtained entirely negative results from their numerous experiments on animals (Hall⁴⁵).

The histology of encephalitis lethargica as observed in the experimental disease differs somewhat from that found in the original infection in man. Levaditi and Harvier (Hall⁴⁵) describe two stages in the experimental disease, an acute short polymorphic, and a longer chronic mononuclear. They have found the parenchymatous changes in the cortex to especially affect the region of the hippocampus at the level of the base of the brain, this they call the "elective zone", and the selective affinity of the virus for nerve cells, they state, is clearly shown. Szymanowski⁸⁸ has obtained a virus and observes that however it is introduced into an animal it always becomes localised in the central nervous system travelling along the nerve trunks. The blood and organs, except the liver, do not contain the virus. Loewe and Strauss⁶⁷ (McCartney) find that the chief cerebral changes in the experimental disease in rabbits consist of

a meningeal and perivascular mononuclear cellular infiltration associated with areas of necrosis surrounded by a zone of mononuclear cells and Kling⁶⁷ (McCartney⁶⁷) reports that 50-60% of inoculated⁸ rabbits show these cerebral changes. But Bull⁸ investigating the relationship of the virus of poliomyelitis to the streptococcus found meningitis and perivascular infiltration in the brain of a stock rabbit which died without inoculation and McCartney⁶⁷ examined the brains of 372 rabbits which were considered healthy or had died of snuffles or which had been experimented upon with tumour transplants and found 55% to show mononuclear infiltration either perivascular, subependymal, meningeal, or cortical and focal necrotic areas in the cortex and he compares these with the histological changes described by Loewe and Strauss, and Kling and his co-workers, and finds them almost identical.

⁷⁴ McIntosh suggests that intracerebral inoculation of rabbits may be of value in the diagnosis of encephalitis lethargica. He finds the emulsion of the basal nuclei is usually positive, and the cerebro-spinal fluid is positive in one case out of four. The rabbits should be killed ten or twenty days after inoculation and the brain examined, the important features to note are the site of the lesions, the nature of the cells, and the presence of small foci of cells in the brain substance.

By his experimental results McIntosh showed in 1919 that the disease was caused by a living virus, probably filterable. Since then Levaditi Harvier and Nicolau, and Strauss Hirshfeld and Loewe have brought forward evidence confirming this view. Levaditi and Harvier (MacNalty⁷⁸) have isolated a filterable virus which can pass wholly or partially through Chamberland filters Nos.1 and 3 from the central nervous system of a rabbit inoculated with brain emulsion from a case of encephalitis lethargica (Paris 1919-20). This they call their "virus C." It can be preserved for a long period in glycerine solution, is destroyed at 56°C, is killed by prolonged contact with phenol, and preserves its virulence for at least forty-eight hours after death. They have not been able to cultivate the organism on Noguchi's medium. Levaditi Harvier and Nicolau find that (1) The serum of a convalescent case of encephalitis lethargica mixed with virus solution and inoculated on to the cornea of a rabbit prevents the development of keratitis and encephalitis, and that the serum of sheep inoculated with brain emulsion from rabbits which have died of encephalitis lethargica neutralises the virus in vitro. (2) Anaesthetics increase the pathogenicity of the virus

inoculated intracerebrally, and (3) - a. Prolonged centrifugalisation of brain emulsion of the virus does not diminish the pathogenicity of the supernatant fluid, - b. Virus emulsion is still active in $1/1000$ dilution, - c. The virus dried in vacuo or mixed with milk is still pathogenic after forty days at room temperature, - d. Pieces of virulent brain in glycerine do not contaminate normal brain or tissues in contact with it, showing that the virus is not diffusible. They found this virus in the central nervous system in cases of encephalitis lethargica, but not in the blood, cerebro-spinal fluid, organs or salivary glands. Immunity can be produced artificially by dead or alive vaccines, but it is not absolute, and the serum of vaccinated animals or of encephalitis patients have no immunising properties, nor are they microbicidal. From further experiments they have obtained from the nasopharyngeal secretions of encephalitis lethargica patients a virus which when inoculated on to the cornea of a rabbit produces encephalitis lethargica, and it can be transmitted in series by corneal inoculations. This they call their "virus fixe". They find further that the mouse is susceptible to infection by intracerebral, peritoneal, or subcutaneous injection, and that in the experimental animal the incubation period is two to three days, that it is

shortened by anaesthetics, and that a polymorphic leucocytosis occurs prior to the initial pyrexia. This virus can be preserved for a long time dry or in water or milk, it is destroyed by bile, certain dyes and antiseptics (e.g. methylene blue and potassium permanganate $1/1000.$), it is pathological for the rabbit intramuscularly, intraperitoneally, or by the corneal route. Corneal inoculation produces a corneal pustule, kerato-conjunctivitis, and encephalitis. The organism has a marked affinity for epithelium.

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Strauss Hirshfeld and Loewe (MacNalty)

have also obtained a filterable virus from the nasopharyngeal membranes in fatal cases of encephalitis lethargica which they consider the specific agent. Their virus has been passed in series through rabbits and monkeys. It can be preserved for many months in 50% glycerol. By using the ascitic-tissue culture methods perfected by Noguchi they have been able to cultivate a minute filterable organism from cases of lethargic encephalitis. This organism is present in the brain, nasopharyngeal mucous membrane, nasopharyngeal washings, cerebro-spinal fluid, and blood. A successful growth is usually manifest on the fifth to seventh day by clouding of the medium.

Fluid cultures under dark-field illumination show the organisms as minute globular refractile forms, occurring singly, doubly or in chains or clumps. The latter forms predominate especially in older cultures. They show active Brownian movement but no true motility. The organism has an average diameter of 0.25 mikrons, may be Gram-positive or Gram-negative, and stains by Giemsa (how it stains is not stated) and methylene blue. Thalhimer confirms these findings, but others do not. Kling and Lilienquist in Sweden claim to have found the virus of encephalitis lethargica in the nasopharyngeal secretions and the intestinal contents.

With regard to the mode of spread Strauss Hirshfeld and Loewe (Hall⁴⁵) in 1919 showed that the virus could be found in the nasopharyngeal secretions of patients with encephalitis lethargica, and Levaditi⁷⁸ and Harvier have shown that infection can be transmitted in animals through the nasal mucosa provided it is previously inflamed or abraded. Levaditi⁴⁵ Harvier and Nicolau (Hall⁴⁵) have obtained a virus from the mixed saliva of normal persons capable of producing a corneal reaction in rabbits. This result has been proved not to be due to any culturable organism in the saliva nor to any spirilla or spirochaete. The virus was filterable and not present in the saliva secreted from the parotid

gland. It appears to live in contact with the formed elements of the mixed saliva, especially the mouth epithelium.

An important point in relation to the carrier theory of infection is the fact that Levaditi⁷⁸ Harvier and Nicolau (MacNalty) have found a filterable virus identical with that of encephalitis lethargica in the saliva of healthy subjects who have never had encephalitis lethargica. This virus has a variable pathogenicity by corneal inoculation, it is present as a saprophyte of the mouth in contact with epithelial cells. They found that 80% were only "keratogenous", while only 15% were "encephalitogenous". The latter could be transmitted indefinitely by corneal or intracerebral passage. From their experiments these investigators have now obtained three viruses. 1. Their keratogenous salivary virus, 2. Their virus of the carrier, and 3. Their virus of encephalitis lethargica of which they have two strains (a) "Virus C" from the central nervous system and (b) "Virus fixe" from the nasopharyngeal secretions.

In 1913 Gruter (Hall⁴⁵) succeeded in transferring the serum from human corneal herpes to the rabbit's cornea. From their experiments,⁸⁸ Loewenstern, Blanc, Doerr, and Levaditi (Szymanowski)

have proved that the ordinary vesicle of herpes febrilis contains a filterable virus infective to the rabbit, guinea-pig, and mouse. Corneal inoculation produces vesicles, conjunctivitis, and conjuncival discharge. The virus can be transmitted from cornea to cornea, and there are no other organisms in the discharge. They have found that this discharge if diluted, passed through a porcelain filter, and inoculated into the brain of a rabbit, produces typical encephalitis lethargica and death; that it can be transmitted in series, can be preserved in 50% glycerine, and is destroyed by heat at 50°C. for half an hour (Hall⁴⁵). They believe that the viruses of herpes febrilis and encephalitis lethargica are closely related, if not identical. Inoculation of the cornea with the virus of herpes febrilis immunised to intradural inoculation with the virus of encephal-
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 -itis lethargica and vice versa. Szymanowski found that corneal inoculation of the rabbit with the virus of herpes febrilis produced conjunctivitis, conjunctival discharge, acute and chronic symptoms and death. Post mortem he found encephalitis and changes in the liver. There was a mononuclear cellular infiltration round the small bile ducts penetrating between the epithelial cells which were proliferated. The liver was congested, and the cells round the blood vessels often destroyed.

Inoculation with emulsion of the liver produced encephalitis in rabbits showing the presence of the virus. ²⁹ Economo considers that the etiology of herpes febrilis and encephalitis lethargica is probably the same, but that in the latter the virulence is much greater for some unknown reason.

²⁵ De Fano found the virus of herpes febrilis capable of producing a fatal meningo-encephalitis in animals almost identical with encephalitis lethargica. The infection was transmissible in series to other animals, some of which recovered and were found to be immune to further injection. He states that the virus has a distinct affinity for the central nervous system, and behaves in many ways similarly to the virus of encephalitis lethargica, and believes that they probably belong to the same group of pathological agents. ⁴⁵ Levaditi Harvier and Nicolau (Hall) found ~~hopes~~^{es} distinctly rare in encephalitis lethargica, but the patients were not immune to the herpetic virus. They have found that the virus of herpes febrilis varies in its power to produce encephalitis by the corneal route, sometimes it fails to do so. The virus of encephalitis lethargica invariably produces encephalitis but if preserved in glycerine for 89 days it produces encephalitis lethargica without keratitis. They conclude that encephalitis

lethargica is caused by a filterable specific virus existing in three forms: 1. Attenuated in the mixed saliva of healthy persons, apparently attached to the buccal epithelium. Affinity epitheliotrope, power only keratogenous. 2. More virulent in the vesicles of herpes febrilis. Affinity epitheliotrope but it is a facultative neurotrope increased by passage. 3. Very virulent in the saliva of carriers, and in the central nervous system of cases of encephalitis lethargica. Both epitheliotrope and neurotrope. They believe that before 1917 it existed as one and two and then for some unknown reason more or less abruptly acquired a new power of attacking the brain easily.

To briefly summarise these findings the macroscopic changes are confined to the brain, and consist of congestion and minute haemorrhages which give the grey matter a pink mottled appearance. Microscopically the vascular changes consist of an infiltration of the adventitia with lymphocytes and plasma cells. The vessels are often dilated and engorged and small haemorrhages are common, while infarction and venous thrombosis are sometimes present. Calcification of the vessel walls and calcified granules in the parenchyma have been observed as early as the fourth day.

The interstitial changes consist of foci of cells composed of lymphocytes and plasma cells, and oedema of the brain substance is sometimes present. The nerve cells show signs of slight toxic degeneration and there is proliferation of the neuroglial cells. Neuronophagia is very rare. A granular black pigment-like material has occasionally been observed in the nerve cells. The sites most affected are the basal ganglia and the grey matter of the mid-brain and pons, but changes may be present in any part of the brain or cord. The lesion is inflammatory, but appears to be a slow process taking a week or more after the onset of symptoms to become fully developed. "Minute bodies" have been observed within and without certain groups of nerve cells, but their significance is not known. Bacteriologically diplococci and streptococci have been isolated from a few cases, but these are probably contaminations. Certain animal experimenters claim to have transmitted the disease to monkeys and rabbits by inoculation of brain emulsion from fatal cases and by inoculation with the nasal washings from patients. The symptoms produced in these animals were not those of encephalitis lethargica as seen in man and it is very doubtful if their claim can be upheld especially as

a large number of experimenters have obtained entirely negative results. The lesions in the experimental disease have been found to especially affect the hippocampus at the level of the base of the brain, and in rabbits consist of meningeal and perivascular mononuclear cellular infiltration with areas of necrosis surrounded by a zone of mononuclear cells. These changes have been found in 50-60% of inoculated rabbits, but have also been found in 55% of stock rabbits which rather takes away from their significance. It has been suggested that intracerebral inoculation of rabbits may be of value in diagnosis.

Levaditi and Harvier claim to have isolated a filterable virus from the central nervous system of a rabbit inoculated with brain emulsion from a fatal case of encephalitis lethargica (virus C.) and from the nasopharyngeal washings of encephalitis patients they claim to have obtained a virus which when inoculated on to the cornea of a rabbit produces encephalitis and it can be transmitted in series by corneal inoculation (virus fixe), and they find the mouse susceptible to this virus. Strauss Hirshfeld and Loewe also claim to have obtained a filterable virus from the nasopharynx of fatal cases of encephalitis lethargica, to have passed it in series

through rabbits and monkeys, and to have been able to cultivate it by Noguchi's method. These findings have not been confirmed by others.

Indicating the probable mode of spread Strauss Hirshfeld and Loewe showed that the virus was present in the nasopharyngeal secretions of patients with encephalitis lethargica, and Levaditi and Harvier have shown that infection can be transmitted to animals by the abraded nasal mucosa. Levaditi Harvier and Nicolau have obtained a filterable virus from the mixed saliva of normal persons capable of producing a corneal reaction in rabbits.

As evidence for the carrier theory of infection Levaditi Harvier and Nicolau claim to have obtained a filterable virus identical with that of encephalitis lethargica from the saliva of healthy persons; it has a variable pathogenicity 80% "keratogenous" and 15% "encephalitogenous". As numerous other investigators have been unable to confirm these findings too much stress must not be laid on them. The virus of herpes febrilis appears to be closely allied to that of encephalitis lethargica, and it can sometimes produce a fatal encephalitis by corneal inoculation in rabbits.

SYMPTOMS.

The central nervous system is so complex in structure and the functions of its various parts are so highly specialised that it is naturally to be expected that an inflammatory disease affecting it should give rise to an infinite variety of symptoms. Any of the functions of the brain or spinal cord may be deranged as a result of the lesions so that it is not surprising that the symptomatology may be very protean. Some sort of classification of such a disease into various types is almost essential, and many schemes have been suggested. A classification on a clinical basis has been found to be impossible as there are almost as many clinical types as there are symptoms.

The classification of encephalitis lethargica which has been generally accepted as being most practicable and scientific is that put forward by MacNalty on an anatomical basis with certain modifications on the lines suggested by Walshe. MacNalty describes three types.

1. General disturbance of the functions of the central nervous system without localising signs.

2. Types with localising signs,

- (a) Affections of the third cranial nerves.
- (b) Affections of the brain stem and bulb with local lesions of other cranial nerves.
- (c) Affections of the long tracts (pyramidal, prepyramidal, and afferent).
- (d) Ataxic types (cerebellum), (e) Affections of the cortex, (f) Involvement of the spinal cord,
- (g) Polyneuritic types.

3. Mild or abortive types with or without localising signs in the central nervous system.

MacNalty⁵⁸ found that in the first epidemic in England 75% of the cases were of the oculo-lethargic type, that is type 2a.

⁹¹Walshe arranges the symptoms of diseases of the nervous system such as poliomyelitis and encephalitis lethargica in the following groups.

A. General Signs of toxi-infection - Fever, shivering, cutaneous eruptions, pains and malaise, gastrointestinal disorders such as vomiting, constipation and foul tongue.

B. Nervous - 1. General, (a) Positive - Insomnia, delirium, mania, restlessness, hallucinations and delusions. (b) Negative - Lethargy coma. -
2. Localising, (a) Positive - convulsions, involuntary movements and muscular contractions, rigidity, ataxia

pain, hyperaesthesia, (b) Negative - Paresis, paralysis, anaesthesia. "Positive" symptoms are the expression of exalted function either from irritation or loss of higher control, and "negative" symptoms express loss or depression of function from destruction of nervous structures or otherwise. Cases may also be classified as acute, subacute, and chronic as suggested by Gullan⁴¹ who describes chronic encephalitis lethargica as an encephalitis with a non-febrile course.

The onset may be sudden or gradual. In some cases its suddenness is dramatic. Apoplectiform symptoms may develop suddenly. Buzzard and Green-¹²field's patient XX suddenly fell down unconscious, and Gullan's⁴¹ case XVIII complained of headache and suddenly fell down semiconscious and appeared to have an apoplexy. A lady stenographer suddenly fell down unconscious while watching a football match and was still unconscious when she arrived at the hospital in the ambulance; she eventually recovered. Gullan's⁴¹ patient XXXVII was suddenly struck down with headache and vertigo while riding a bicycle and found lying by the road side in a collapsed condition. Epileptic convulsions or syncope have been the first evidence of the disease in some cases. Of Crookshank's¹⁹

127 cases 36 had a sudden onset and 17 a gradual, while Findlay³³ describes a sudden onset with or without fever in 23 cases in children, and Chalmers and Macgregor¹⁶ found a sudden onset frequent in their cases. Gullan⁴¹ reports 62 cases of which 27 had a sudden onset, 15 an onset which might be described as "quick", and in 20 cases the onset was over eight days.

A gradual onset is, however, commoner, though the day on which symptoms were first noticed can often be definitely stated. MacNalty⁵⁸ and Bramwell⁶ describe a prodromal period before the acute stage, and found lethargy, headache, giddiness, and diplopia the most common prodromal symptoms, but almost any symptom may be complained of, and lassitude and conjunctivitis were fairly common. The prodromal period is usually one to seven days, but may be as long as three weeks. Three of my cases showed a definite prodromal period.

Case 1. male aet. 19, cotton operative, seen on January 29th 1926. Two weeks before he had had severe constant headache, and frequently saw things double. He kept at work for a week, and then had to give up owing to drowsiness and headache. During the previous week he had had severe headache, somnolence, and excessive salivation, but had not

seen double again. He sat without moving for hours at a time, "as if in a trance". On examination he had bilateral facial paresis, especially affecting the right side. Lacrymation of both eyes chiefly the right; the tears ran down his cheek on the right side. Temperature 99°. Pulse 92. Slight pharyngitis, not complained of. Nothing else abnormal. On February 10th he was much better, the facial paresis was unaltered, but there was no headache or drowsiness. Excessive salivation was still present. He complained of waking at 2 a.m. every morning and not being able to get off to sleep again. Previously always a sound sleeper, having to be manually roused as a rule. On February 20th he was back at work. Facial paresis and excessive salivation and lacrymation were still present. He was sleeping better in the morning. On March 1st. there was still some right facial paresis, and there was loss of convergence of the eyes and lateral nystagmus especially marked on elevating the eyes.

Case 4 developed severe frontal headache which persisted and a week later gradually increasing drowsiness, and it was not until a month after the first complaint that he had an apparent apoplexy and

pyrexia was observed for the first time. Case 9 had trembling of the arms and legs, pain and stiffness of the back of the neck, and drowsiness for a week before he had to take to his bed.

The onset may take various forms. Five of my cases complained of very severe headache as a prominent initial symptom, and Edgeworth³⁰ found malaise and headache, generally unilateral, the most common symptoms at onset in 20 cases. Buzzard and Greenfield¹² describe neuralgic pains and headache as very common, and found sleeplessness a prominent early symptom, and three fatal cases described by Ellis³¹ commenced with lancinating neuralgic pains and fever. Nocturnal insomnia and excitement with diurnal somnolence was the first complaint in a boy of 9 described by Fletcher³⁴ and two of my cases showed a similar onset; they were both boys aged 8 and 9 years respectively. An onset simulating epidemic influenza is fairly common and Wilson⁹⁵ and Buzzard and Greenfield¹² have described such cases. Three of the present series commenced with what was diagnosed at the time as "influenza" but they all had drowsiness and severe headache and one case complained of diplopia. Weber⁹³ saw a girl of 19 whose initial symptoms were myoclonic or choreiform twitchings

especially affecting the left side with excitement
 and mental wanderings, and Hall⁴⁴ states that
 general extreme asthenia, acute mental symptoms,
 mania, delusional insanity, confusional states, a
 delirium tremens like condition, or excito-motor
 phenomena of all kinds may be the first evidences of
 the disease. Vomiting and severe constipation are
 fairly common but Hume Nattrass and Shaw⁵¹ saw acute
 diarrhoea at onset in a fatal case. Bramwell⁶
 mentions vomiting as one of the commoner early
 symptoms and Chalmers and Macgregor¹⁶ found it
 occasionally present. It occurred in 38 of the cases
 investigated by Crookshank¹⁹ and in 10% of those
 reported by MacNalty⁵⁸. Buzzard and Greenfield¹²
 saw two cases with gradually developing spasms of the
 right side followed by paralysis and aphasia,
 simulating cerebral tumour. Many cases have a
 gradual and insidious onset with no history of fever,
 and appear to be very chronic in type. Thus my case
 7 had no illness for some years previous to a
 gradually developing persistent nocturnal insomnia
 which continued for nine months and was followed by
 ten months of weakness and lassitude. During all this
 time she was working as a stenographer and found it
 quite possible to continue her duties in spite of the
 insomnia and lassitude.

Following the prodromal period, which may last only a few hours, the declared symptoms of a general infectious disease become manifest, ushered in as a rule by pyrexia, which, however, only very rarely plays a prominent part in the disease.

⁵⁸ MacNalty found pyrexia present in 76% of cases, and states that it was a constant symptom in every case which had come under detailed observation from the onset, indicating that it may be of such short duration that unless the temperature is frequently recorded it may be missed altogether. On the other hand ⁴¹ Gullan found no fever at all in over 50% of his cases, and there is no doubt that many slight cases, and cases of what has been described as the chronic type are apyrexial throughout. Buzzard and ¹² Greenfield describe five cases (No. 4 to 9) which were all slight and easily missed with no pyrexia or general disturbance, and complete recovery in a few weeks or months, and Chalmers and Macgregor ¹⁶ found that in Glasgow in 1920 there were many cases with very little fever. The temperature rises to 101° or 102° , rarely to 103° or 104° as in Buzzard and Greenfield's ¹² case 1. Hyperpyrexia occurs in a few cases and is usually fatal but Gelpke (Hall ⁴⁴) recorded a temperature of 111° in a case that recovered. Pyrexia usually lasts from two to five

days, but may continue as long as ten or fourteen days; Chalmers and Macgregor¹⁶ found it continuous at first and later intermittent. The pulse is usually found to be accelerated in direct ratio to the amount of fever present, but Gullan⁴¹ noted a rapid pulse in a number of afebrile cases.

Headache is an especially common and prominent early symptom. It may be only slight or very severe, and is often very persistent. It may be frontal or occipital, and is frequently unilateral. Chalmers and Macgregor¹⁶ found marked headache a common symptom in their cases, and MacNalty⁵⁸ found headache, usually frontal, complained of in 70% of the 1918 cases in England. Vertigo has been observed frequently in the early stages by Bramwell⁶ and Chalmers and Macgregor¹⁶, and it was complained of by 30% of the cases reported on by MacNalty. It may be the first symptom as in Gullan's⁴¹ case 37.

General asthenia is frequently very marked and the weakness may amount to complete prostration so that the patient lies helplessly in bed and can hardly move a muscle; in other cases it only amounts to a feeling of lassitude, but MacNalty⁵⁸ found muscular weakness to a greater or less extent in all his cases. Bramwell⁵ found extreme asthenia common and considered it a very serious feature.

As its name indicates encephalitis lethargica has lethargy as perhaps the most common symptom. Although some degree of lethargy at some period of the illness is the rule in a certain number of cases, there is no evidence of the slightest drowsiness throughout. Lethargy and somnolence have been mentioned as especially frequent early symptoms and Chalmers and MacGregor¹⁶ found that the lethargy might be early or late, in the latter case succeeding an irritable stage, and that in some it was not a prominent feature but in the great majority it was present in a greater or lesser degree. Graham Forbes⁴⁴ (Hall) found lethargy present in 126 out of 130 cases. Gullan⁴¹ found lethargy and stupor to be the most common symptoms in a large number of cases and in 1918 MacNalty⁵⁸ found 80% of the cases were lethargic. Melland⁷⁶ writing in 1921 states: "In some cases, no doubt, lethargy is a most striking feature of the disease, in others, I believe the majority, it is inconspicuous or entirely absent." Lethargy has been a prominent symptom in only two of my cases, and these occurred in 1921 and 1922 before the earlier "negative" phase of the disease had given place to the phase in which "positive" symptoms are more in evidence.

Case 2, male aet. 35, in Ward 31. E.R.I. 1921. He was completely lethargic for three weeks and could only be roused by shaking and shouting. When awakened he complained of seeing things double and severe pain in the right forehead. No strabismus or ocular palsies were found on examination. When last seen he was up and about and the pain and diplopia were gone. He had been put on large doses of strychnine just before and this had relieved the symptoms, especially the lethargy.

Case 3, male aet. 40, in Edinburgh Fever Hospital 1922. He was lethargic, and lay like a log, with immobile features and a mask-like face. He was easily roused and could answer questions intelligently but mumbled his answers.

The degree of lethargy varies considerably in different cases; in some it only amounts to a feeling of drowsiness and somnolence, which can be resisted sufficiently to enable the patient to carry on his ordinary duties. A very common type of lethargy is what is called lucid-somnolence, a somnolence from which the patient can easily be roused to feed or answer questions, but when undisturbed he again quickly lapses into stupor; he seems unable to rouse himself, but knows all that goes on around him. Stallybrass⁸⁶ found this a prominent

symptom in Liverpool in 1921. It is sometimes surprising how quickly a stuporose patient answers questions, others are irritable when awakened, while in others the lethargy is deeper and a strong external stimulus is required to rouse them. Others again are in a profound stuporose condition, with open eyes, amounting to coma from which it is impossible to rouse them; this is seen usually towards the end of a fatal case, but is sometimes recovered from.

Frequently an initial feeling of drowsiness deepens gradually into the lethargic or stuporose condition, but even in cases with profound stupor, true

refreshing sleep is often not obtained and the patient suffers from insomnia (MacNalty⁵⁸). Of

¹⁹Crookshank's 127 cases drowsiness was noted in 30, stupor in 26, and unconsciousness or coma in 25. In

³⁶Fyfe's four cases the chief complaints were somnolence and headache, but they were all ambulatory

throughout. Although only two of my cases have suffered from severe lethargy, drowsiness, in some degree, has been complained of by eight others, and consisted of falling asleep at meals and whenever they sat down. In four cases the drowsiness was associated with nocturnal insomnia and three of these had severe nocturnal excitement as well. Lethargy may last only a few days or extend into weeks or months, while some cases have recurrent periods of lethargy for years.

The cause of lethargy is undecided and several suggestions have been put forward. MacNalty⁵⁸ and Bramwell⁵ believe that it is due to an extension of inflammation from the region of the third nerve nuclei to neighbouring afferent paths, thus interfering with stimuli to the thalamus. This, I think, is the most generally accepted view and, in my opinion, is the cause of lethargy, while nocturnal insomnia, I would suggest, is due to a lesion of a centre in the brain, probably thalamic, controlling the rhythm of sleep, the two lesions being quite separate. Buzzard¹⁴, however, suggests that lethargy may possibly be attributed to a condition of hydrocephalus induced by inflammation and oedema around the aqueduct of Sylvius interfering with drainage of the cerebro-spinal fluid from the third and lateral ventricles. Marinesco (Hall⁴⁴) considers the lethargy as a part of the marked tonus changes which are so often present. Economo²⁹ believes the functions of sleep and awakening are controlled by a focus in the brain very near the centre for ocular movements, and that encephalitic lesions of this focus produce changes in the rhythm and duration of sleep - e.g. months of day-light sleep. Disordered hypophyseal function, leading to hypopituitarism, has been suggested on the grounds that lethargy is a symptom of this defect and that polyuria, obesity,

and even Frohlich's syndrome have followed encephalitis (Hall⁴⁴). Abrahamson¹, in a very wordy article, propounds the theory that lethargy is due to a toxic increase of resistance of the synapses of the psychic cells.

What is described as early Parkinsonism to distinguish it from the condition as it is seen in the later stages of the disease, is a very frequent and characteristic manifestation indicating a lesion of the red nucleus or rubrospinal tract (Bramwell⁵). One of Hall's⁴² first cases in 1918 was a woman of 56 with Parkinson's mask and muscular tremors, and he noted in the same series that the lethargy was associated with a peculiar posture of the hands across the trunk and an abnormal plastic tone in the muscles, while Buzzard¹⁰ saw a man of 54 who lay in bed in a state of general rigidity presenting every appearance of advanced paralysis agitans, including the mask-like face and the characteristic attitude of the limbs, and his¹² case 5 was ambulatory, with diplopia and somnolence followed by slight Parkinsonism which cleared up in two months. Bramwell⁶ describes the appearance of a typical case thus. He lies flat on his back motionless for hours, the face is flushed and the eyes half closed, he is disorientated and takes no

interest in his surroundings and makes no complaint. When he is spoken to, the lips move but the face remains immobile and featureless, and the response is very slow. There is often marked tremor, fumbling with the bed clothes or jerking movements, and delirium and sleeplessness may be present.

Somnolence may deepen to coma. Gullan⁴¹ observed athetosis in a small proportion of cases. Stallybrass⁸⁶ noted especially the mask-like facies expressing the patient's mental apathy; MacNalty⁵⁸ found this to be accentuated in cases with facial diplegia but it might occur independent of it, he found the arms sometimes extended, sometimes flexed across the chest or abdomen, and the hands were often held with the metacarpo-phalangeal joints flexed and the inter-phalangeal joints extended in the accoucheur's position, he frequently observed fibrillary twitches of the face and tremulous movements of the lips, and states that the severest cases lie like logs or resemble waxen images in lack of expression and immobility which may be accompanied by catalepsy including *flexibilitas cerea*. The alteration in the voice, in cases with Parkinsonism, is very characteristic. There are two types of speech change, type one is a hesitating, slow, slurring, monotonous, nasal voice, and type two is the same

only sometimes for a short period speech will be so quick as to be unintelligible.

As any part of the nervous system may be involved the localising signs which may be produced are almost unlimited. Cranial nerve palsies may be complete or incomplete, may affect one or more nerves on one or both sides. When bilateral they are not symmetrical in extent or time of onset. They alter from day to day, while one is getting worse another is clearing up, and they often disappear as quickly as they come. This progressive and transient character is pathognomonic of encephalitis lethargica.

³⁰ Edgeworth found the cranial nerves affected in 19 out of 20 cases. The third, fourth and sixth nerves are those most frequently involved. As a rule the change is a disturbance of muscular synergy producing mystagmoid movements, irregular jerks of the eye muscles, or diplopia, although a true strabismus sometimes occurs. Incomplete bilateral ptosis and pupillary disorders such as fixation, inequality, irregularities, and cycloplegia have been observed. These changes vary from day to day, and affect different nerves at different times. Bilateral paralysis of accommodation is not uncommon. Bramwell⁵ considers that nystagmus may be due to involvement of the direct nerve supply to the ocular muscles or of the posterior longitudinal bundle. Chalmers and

Macgregor¹⁶, Stallybrass⁸⁶, and Gullan⁴¹ found external ophthalmoplegia very common, producing especially nystagmus, ptosis, diplopia, and strabismus in that order of frequency, and internal ophthalmoplegia was also sometimes present. Gullan⁴¹ noted some degree of nystagmus in 90% of cases.

The facial nerve is the next most frequently involved and both sides are as a rule affected, though one side is usually more affected than the other. The optic nerve is very rarely affected but Melland⁷⁶ has frequently observed optic neuritis and Findlay³³ found marked congestion of the optic discs in the early stages in some of 23 cases in children, while Buzzard¹⁴ states that slight papilloedema may occur in the acute stage due to increased intracranial pressure. Crookshank¹⁹ found amaurosis with slight changes in the papillae in five cases, and MacNalty⁵⁸ reports that of fifty cases examined, in no case was true papilloedema seen. The fifth nerve is frequently involved and weakness of the masticatory muscles is common. The auditory nerve is sometimes affected, Crookshank¹⁹ and Gullan⁴¹ have reported such cases. Dysphagia has frequently occurred. It was a troublesome symptom in 23 of MacNalty's⁵⁸ cases. It was also observed by Crookshank¹⁹, Stallybrass⁸⁶, and Bramwell⁵.

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Sarkies saw a medical man with attacks of laryngeal spasm lasting 48 hours, followed by an uninterrupted recovery. Denyer and Morley²⁸ report a case with extreme laryngeal spasm causing dysphagia, so severe as to result in rupture of a constrictor muscle, subcutaneous emphysema, and aspiration pneumonia.

Paralysis of the palate has been observed by Edgeworth³⁰ and Hall⁴³. MacNalty⁵⁸ reports one case with paralysis of the spinal accessory nerve.

Hypoglossal palsy is not uncommon and has been observed by Crookshank¹⁹ and Hall⁴³, hemiatrophy of the tongue may result. In a case recorded by Schmidt (Hall⁴⁴) the tongue was rigidly projected over the teeth, necessitating surgical measures to give relief. Aphasia has been observed in a large number of cases. Localised nerve pains, which may be of thalamic or spinal origin, have been very common. Abrahamson¹ had a case with pain in the occiput and left shoulder persisting from the onset. Bramwell⁵ found neuralgic pains in the head and limbs very often the chief complaint. Gullan⁴¹ saw a man of 33 with shooting pains down the legs and in the back and head, who in three months was entirely free from pain, and hyperaesthesia, especially plantar, was observed by MacNalty⁵⁸. Some cases show symptoms of cerebral irritation followed by paralysis indicating a cortical lesion.

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Walshe saw a case with right-sided Jacksonian fits, starting in the thumb and worst in the hand and arm, followed by progressive right hemiparesis. Buzzard¹² Greenfield¹² recorded three such cases (Nos. 17, 18, and 20), while cases simulating cerebral haemorrhage and producing hemiplegia have been very frequently recorded, such as Buzzard and Greenfield's¹² case 20. Bramwell⁵ also saw such cases, and Gullan⁴¹ saw three cases simulating apoplexy and one simulating haemorrhage into the pons. One of my series resembled cerebral haemorrhage.

Case 4, male aet. 45, grocer. On August 18th 1925 he complained of severe headache confined to the right frontal region. This persisted without change, and during the next week he began to lose interest in and neglect his work. He found difficulty in keeping awake, if he sat down he was asleep in a minute, he became careless in his dress and suspicious about his wife's absences. He sat about for hours asleep or doing nothing, and when questioned mumbled his answers. He fell asleep over his food, could not pick up a cup of tea without spilling most of it, and had to be fed at every meal. On two occasions he got out of bed in the middle of the night and turned

the gas full on, so that his wife had to get out and turn it down again. Examined at this time, August 29th, he had a bad colour, was very sallow with dark rings round his eyes; he was sitting passively with a vacant expression, and dressed clumsily as if in haste. He answered questions slowly and indistinctly, and said he felt ill; the tongue was covered with a white fur, and the temperature was normal. Systolic blood pressure was 100 m.m. The heart and lungs were normal and the other organs in good health. The pupils were equal and reacted rather sluggishly to light, the knee-jerks brisk, and ankle clonus was present on the left side. No Babinski's sign, no optic neuritis. On September 2nd. he went into town, five miles away, by tramcar on business and was brought back by a friend who said he had seemed lost and unfit to go about alone, and that he had noticed a twitching of his face. While in town he had evidently fallen, for he came home with a "black" eye. On September 15th he went a walk of two miles with his sister. On Wednesday September 16th he was going upstairs, slowly as usual. When he was four steps from the bottom his wife called to him to know what he was going upstairs for, he turned round to come down again and fell headlong to the bottom. When seen about half an hour later he was only semiconscious

and showed distinct paralysis of the right arm and leg, but not of the face, the pupils were equal and the temperature 100⁰ F. On the following day he became more conscious, but the right arm and leg were both completely paralysed, the temperature normal, and the tongue very thickly coated with a brown fur. He was slightly delirious. The hemiplegia rapidly improved in the course of a few days, and on Sunday 24th September he was out of bed for a short time but in the evening had a sudden recurrence of it while in bed and was unconscious for a short time. The paralysis of the right arm and leg were complete, no active movements whatever being possible, exaggerated reflexes, Babinski's sign, and ankle clonus, were accompanied by spasticity. On Tuesday 26th September he suddenly became very pale and pulseless and the heart was only beating very feebly, but he was conscious. On October 3rd. he became unconscious and there was difficulty in getting him to swallow food or drink. He became pulseless on October 6th and very gradually sank and died on October 10th 1925, seven weeks after the first symptom. There was no autopsy. A quinsy in 1918 was the only previous illness that could be remembered. The possibility of the first hemiplegia being due to the fall suggests itself, but the fact that there was no sign

of external injury to the head and that the second occurred while the patient was in bed undoubtedly excludes it, while the very rapid improvement suggests an inflammatory rather than a traumatic lesion.

Hemianaesthesia and hemianopia have been observed by Meyer⁷⁷ and Buzzard and Greenfield¹², and ataxia occasionally occurs when the cerebral peduncles or cerebellum are involved. Gullan⁴¹ saw a woman with definite ataxia of the arms and legs after the acute stage. Signs of meningeal irritation may be present, and even in his first series of cases Hall⁴² divided them into the meningitic and the asthenic, and found the former to simulate meningitis so closely that at a certain stage it was almost impossible to make the distinction except by examination of the cerebrospinal fluid, and the fact that in a few days the symptoms subsided and improvement set in. Mc Caw⁶⁸ saw six cases corresponding to the meningitic type described by Hall. Bramwell⁵ also found meningitis closely simulated in a number of cases, while Gullan⁴¹ saw several cases with head retraction with or without rigidity and stiffness in the limbs, and one case with exaggerated reflexes and positive Kernig's and Babinski's signs. Crookshank¹⁹ observed head retraction in 23 cases. Evidence of spinal cord involvement is seen in some cases. Wright⁹⁷ recently reported a woman who had drowsiness, diplopia

retention of urine, and complete flaccid paralysis of both legs with anaesthesia up to the level of the third ribs. At the time of writing she was slowly improving and could walk a little with a stick.

Retention of urine was observed by Ellis³¹ in all⁵⁸ of a series of three fatal cases. MacNalty³⁰ saw seven cases with peripheral neuritis. Edgeworth saw a case with paresis of the right arm and leg with loss of reflexes indicating a polyneuritis.

Although "positive" symptoms were present in isolated cases during the first outbreak, they then held no prominent place in the clinical picture.

Of Crookshank's¹⁹ cases, tremors, twitchings, or choreiform movements were observed in 22. In 1918⁶⁸ Mc Caw saw a girl of 13 with coarse tremor of the hands and irritable movements of the legs, and⁵⁸ MacNalty⁵⁸ noted twitchings of the face and limbs and found rapid rhythmic tremor accentuated by exertion or emotion common throughout, while violent jerking movements of the body and limbs almost like epileptic convulsions were seen in certain cases and non-rhythmic irregular spontaneous choreiform movements of the face, trunk, or limbs not infrequently appeared late and persisted for some time. Buzzard and Greenfield¹² noted involuntary muscular movements of the arms and legs in their cases 10, 11, and 12.

In January 1919 Poynton⁸² showed a girl of three with generalised myoclonus who became ill in October 1918. There was a rapid coarse tremor of all the muscles of the body increased by external stimulation.
⁴Boveri in 1920 reported a girl of 19 with short rhythmic contractions, 66 per minute, of the flexors of the arms, and of the right quadriceps and the diaphragm, present during sleep, and a woman of 40 with rapid rhythmic muscular contractions of the right sterno-mastoid and trapezins and of the diaphragm, 48 per minute, and later of the abdominal wall and right abductor femoris and sartorius. He suggests that encephalitis lethargica might conveniently be divided into two types, the myoclonic and the lethargic.

The change of type in which the "positive" symptoms became more prominent was observed in Italy and France as early as 1919, but Ellis³¹ was the first to report^{it} in England when in July 1920 he described three fatal cases of acute myoclonic encephalitis. Since then large numbers have been seen in all parts of the world. The movements observed were short, rapid, explosive, rhythmical muscular contractions resembling those produced by electric stimulation. The rhythm was irregular and about 30 per minute. The contractions affected

especially the muscles of the abdominal wall, usually the recti, sometimes the obliques. In cases 2 and 3 the rhythmic contractions of the abdominal wall were so forceful as to shake the bed, and affected especially the lateral abdominal muscles, each contraction giving a sudden flattening of the abdomen, a pulling in of the lower ribs, and a sudden jerking upward movement of the pelvis on the affected side. Both sides were affected to some extent, but one usually more than the other. In severe cases the body is jerked from flexion to extension, and vice versa, so that the patient sometimes has to be held to prevent him falling out of bed. Hall⁴³ reported a case with myoclonic contractions of the abdominal muscles simulating an "acute abdomen". The symptoms were severe abdominal pain, and cramp-like spasms of the abdominal muscles with slight pyrexia; recovery took place in a few days.

The name "myoclonus" was first employed by Friedreich (Walshe⁹⁰) in 1881 to describe certain features in a disease he named paramyoclonus multiplex. Oppenheim defines "myoclonus" as, "Clonic contractions of the muscles of the limbs or trunk, rarely of the face; The contractions are short and lightning-like, involving a small number of muscles which do not have a synergic action. Resulting movement of the limb

as a whole is slight or absent; the contractions may be symmetrical, and are not rhythmical but irregular and about 60 to 100 per minute; they may occur in only a part of a muscle, are stopped by active movement and increased by emotion; they stop during sleep". Buzzard and Greenfield¹² believe that the involuntary movements in encephalitis lethargica are probably due to release of some nervous activity by interference with control because they can be temporarily controlled and generally cease when the parts are being voluntarily employed. The fibrillary twitchings and myoclonic contractions in cases 5, 6 and 7 of Walshe's⁹⁰ series were thought to be due to irritation of the lower motor neurones.

In encephalitis lethargica any muscle of the face, trunk, or limbs may be the seat of myoclonic contractions and whole groups of muscles may be affected so that a coordinated series of movements may be performed. They sometimes persist during sleep. Many cases present irregular jerky movements or twitchings and these merge into cases presenting choreiform movements in which chorea gravis is closely mimicked except that the movements persist during sleep. The muscular contractions, as a rule, show an irregular rhythm of between 80 and 100 per minute, they are often associated with severe pains and spasticity. In the Glasgow epidemic of the Spring

of 1920 an irritative stage was seen (Chalmers and Macgregor¹⁶). Restlessness and involuntary muscular movements appeared early but were sometimes delayed a few days or weeks. Spasmodic twitching or choreiform movements involving the feet, limbs, or whole body were a marked feature of most of the cases. Twitching was present in 18 cases, but it may be so slight in others that it is entirely overlooked. Two of Gullan's⁴¹ cases had marked myoclonic contractions of the lower jaw muscles, of varying rhythm but constantly present except during sleep, and Herd's⁴⁹ case 1 had frequent typical eclamptic fits followed by rhythmic clonic contractions of the jaw muscles, while his case 2 had clonic movements of the head and limbs present during sleep. A girl of 19 reported by Weber⁹³ had myoclonic or choreiform twitchings, mostly on the left side, at the onset, followed by lethargy and ending fatally, and Findlay³³ observed choreiform movements followed by lethargy in his 23 cases in children. Stertz⁴⁴ (Hall) reports that 50% of his cases in Munich during the 1920 epidemic had choreiform movements. Hall⁴³ reports a case with violent clonic spasms of the neck and arms and another with a series of left-sided epileptic convulsions with loss of consciousness and pyrexia during convalescence

followed by complete recovery. Hiccough has been frequently observed as in Farrar's⁷⁸ and Sarkie's⁸⁵ cases, and Gullan⁴¹ saw a patient with troublesome hiccough for two weeks, while in Russell Brain's⁸⁴ case it lasted eight days. These indicate a lesion of the cervical region of the cord.

The changes in the reflexes necessarily vary with the location of the lesions in the central nervous system. Hypertonus has been present in a considerable proportion of cases, in association with lethargy and Parkinsonism. It may be general or affect the upper or lower limbs alone, more often the latter.

Insomnia may be a very troublesome and intractable symptom, and it may persist for a long period. Although often associated with lethargy it sometimes occurs alone without any lethargy. Ellis³¹ reports three fatal cases with constant delirium and insomnia and no lethargy throughout. Chalmers and Macgregor¹⁶ found insomnia almost constant; it occurred early in most cases, and might precede the onset of twitching by a few days. In Liverpool in 1923 Stallybrass⁸⁶ found only 45% of the cases lethargic; the remainder were myoclonic, choreiform or psycho-motor in nature.

Instead of lethargy there was insomnia, restlessness,
 excitement, and delirium. As early as 1918 MacNalty⁵⁸
 found that some cases suffered from insomnia without
 any stupor. Nocturnal excitement and diurnal
 somnolence is a frequent symptom, especially in³⁴
 children, and Fletcher saw two boys aet. 9 and 11
 in which it was followed by apparent complete recovery.
 Three of my cases have shown this symptom, all males,
 aet. 8, 9, and 19.

Case 5, male, aet. 19, latter. In October
 1924 he had an acute attack of tonsillitis. For a
 year or two before that he had had frequent attacks
 of acute tonsillitis occurring in large chronically
 inflamed tonsils. In March 1925 he complained of
 somnolence and lassitude for a short time, but was
 not confined to bed and in June he had another attack
 of acute tonsillitis. In July he began to suffer
 from insomnia. Slight at first it gradually became
 worse, and besides insomnia he showed restlessness
 and even excitement. Never having sketched before
 he spent his time at night drawing the most elaborate
 sketches, going into any amount of detail and showing
 considerable skill. At other times he spent the
 night talking, moving about and changing the bed-
 clothes around trying to get a comfortable position
 in which to get to sleep. At these times he would

talk of suicide as a relief from his difficulty. During this time he was at work all day and seemed quite capable of getting on without sleep, going sometimes three days and nights without sleeping an hour. In September 1925 he was particularly sleepless and had the fire alight at three one morning. He spent an hour from two to three a.m. whitewashing the scullery wall on another occasion as it wanted doing and he could not get to sleep. This condition continued from June to October 1925 and in October he contracted scarlet fever. During the first three nights of the scarlatina he slept soundly all night, but when his temperature became normal once more his insomnia and nocturnal excitement started afresh. Examined in November 1925 he showed no abnormal physical signs except diplopia on looking to the right and enlarged tonsils. In every other respect he was physically sound. From October 1925 to January 1926 his condition remained unaltered, but slightly improved; he might have one fairly quiet night out of four. In January 1926 he had another attack of acute tonsillitis, sleeping soundly while feverish but suffering from insomnia on recovery. As regards his temperament, the first change was observed by his mates at work who asked him in May 1925 if his tongue was not sore, he talked so much; he spent all day

chattering away about nothing in particular. Dating from June 1925 he changed from a sociable boy, keen on out-door exercise and male companions, so that he only came home for his meals, to an amiable and chatty helper in the house, always cheerful, much more so than formerly, never wanting to go out of doors, deserting his friends, spending his time cleaning or mending anything in the house that required it, doing it slowly and carefully, and taking his time about it. From June 1925 also his appetite, always good, increased rapidly and he began to eat enormously, was always hungry, and complained of, "too much phlegm in his mouth". In May 1926 he was back at work but the insomnia was unchanged. As regards previous illnesses, apart from repeated attacks of acute tonsillitis, the only one was an operation for removal of extensive tuberculous glands in the neck at the age of three.

Two other cases have had persistent insomnia, and in one of them it was the first symptom and the only one for nine months.

Delirium is a very prominent symptom in many cases, it may only amount to a restless confused state as in the cases reported by Herd⁴⁹, or it may be more severe with delusions and hallucinations, but in some cases it is extreme requiring forcible

control. Of Crookshank's ¹⁹ 127 cases delirium was present in 19, with delusions and hallucinations in 3, and maniacal delirium occurred in 2 cases, Cases with maniacal delirium have been described by Denyer and Morley ²⁸, and Chalmers and Macgregor ¹⁶. MacNalty ⁵⁸ observed that all degrees from muttering to maniacal delirium might occur, but the delirium usually only lasted for the first week, although one of the cases was delirious for five weeks. Delirium is usually more prominent at night, and may be continuous, but frequently alternated with somnolence and stupor. ⁵⁸ MacNalty gives an explanation of this. Stupor, he says, is produced by the cutting off of stimuli from the environment. Normally it is by the perception and appreciation of such stimuli that the conduct of the individual is guided and controlled. These stimuli are inhibited, and, when there is an attempt on the part of the patient toward cerebation and overcoming of the stuporose condition, he is deprived of the perceptions which normally regulate his conduct. Cerebation, reinforced often by subconscious stimuli, no longer repressed, ranges wild and uncontrolled - that is, the patient is delirious.

The delirium has a peculiar feature. It is remarkable, in many cases, how easily the patient can be roused to reason for a short period by a sharply put question or command, and can answer questions or perform actions sensibly whilst spoken to, though there may be some mental confusion in some cases.[~] Such cases of lucid-delirium have been described by Harris⁴⁸, Bramwell⁵, Chalmers and Macgregor¹⁶, Gullan⁴¹, and Stallybrass⁸⁶. The delirium is often dependent, in its subject matter, upon the patient's ordinary duties. Thus a painter continuously performed the actions of painting, and a servant girl got up in the middle of the night and lit the kitchen fire (Stallybrass⁸⁶). Gullan⁴¹ saw twenty-four cases of a similar nature, one of which an ex-police sergeant made signs of traffic control, and Bramwell⁵ has seen a number of cases with occupational delirium.

Vomiting after the prodromal period is very rare, but in one case³⁷ persistent vomiting was present which soon only manifested itself when the patient moved her head to one or other side. This then improved and for a further ten to fourteen days she only vomited if she sat up in bed.

Severe constipation is a very troublesome symptom in a large number of cases, frequently resisting all measures to relieve it for some days. ⁵⁸ MacNalty found it present in every case and Bramwell⁶ mentions it as an especially frequent early symptom. Along with constipation, or even when constipation is absent, the condition of the tongue is of great importance. ⁶⁸ Mc Caw mentions a dry brown tongue in five cases out of a series of six, and Buzzard¹⁰ mentions it in one case. Reynolds⁸³ lays the greatest stress on the condition of the tongue, and goes so far as to say that to diagnose encephalitis lathargica you must think of all the diseases you know of, exclude them all except encephalitis, and if the tongue is foul that is the answer to the question. The tongue is very coated early in the affection, and does not clear up when any pyrexia has disappeared, but continues to appear unhealthy for weeks or months, sometimes during the whole course of the illness; it is swollen and flabby but not tooth-marked; if not coated it is angry-looking and cracked; generally it is over-moist, but sometimes it is dry, cracked, and "typhoid"-like. But in one form or another the foul tongue is ⁵⁸ practically always present. MacNalty mentions similar appearances of the tongue in the earlier cases, and my experience has helped to corroborate Reynold's opinion.

A subacute pharyngitis is a very frequent condition found on examining patients, but it is not as a rule complained of and appears to give rise to very little discomfort. Gardner⁷⁸ describes the condition thus. There is slight swelling but very marked congestion of the fauces and pharynx; the colour is generally a deep crimson but sometimes is almost vermilion. There is comparatively little swelling of the tonsils, but whitish patches of exudate are to be seen on the tonsils, fauces and pharynx. These throats tend soon to become dry, and are often associated with a red, bare, swollen and dryish tongue. Sore throat was a constant symptom⁴¹ of all the cases in the Derby outbreak, and Gullan found severe pharyngitis in many of his cases.

A simple catarrhal conjunctivitis has been frequently observed in the early stages, and in a number of cases it has been the first general symptom of the disease, suggesting that the virus may gain entrance to the brain through the eyes.

A haemorrhagic tendency has been observed in some cases; Buzzard and Greenfield¹² called attention to meningeal haemorrhages, and haemorrhagic cerebro-spinal fluid has been noted. Purpuric eruptions, intestinal haemorrhages, and severe epistaxis have occurred. Tinel and Dupouy (Hall)⁴⁴ have reported two fulminating cases, one with fatal

haematemesis, and the other with terminal nasal, buccal, and intestinal haemorrhages. In each there were multiple ecchymoses.

There is always a slight leucocytosis in the blood during the early part of the illness, but as the acute stage passes off this quickly disappears. Taking the normal leucocyte count as 5 - 6000 in adults, and 8000 in children, Vaidya⁸⁹ finds that in encephalitis lethargica the average is 7000 in adults and 9000 in children. In polio-³¹-myelitis the average is 15 - 30000, but Ellis³⁰ reported three cases of encephalitis lethargica with leucocytoses between 15000 and 21800, and Edgeworth found a leucocytosis of 10320, 25000, and 35000 respectively in three cases during the acute stages.

In pyrexial cases the urine has the properties of febrile urine; it is concentrated, highly coloured, and has an excess of urates; transient albuminuria during the febrile period is common. In cases where urotropin is being exhibited in excess abundant blood and albumen may be found in the urine, but these disappear quickly as a rule when the drug is discontinued.

The cerebro-spinal fluid shows very characteristic changes. In a normal cerebro-spinal fluid the total protein is between 0.013 and 0.02% (average 0.018%), the sugar between 0.048 and 0.058% (average 0.053%), the chlorides between 0.725 and

0.74% (average 0.732%) and the cells, which are all lymphocytes, between 0.5 and 1.5 per cmm. (average 1 per cmm.), over 5 per cmm. being considered abnormal. In encephalitis lethargica (Perdrau⁷⁸) the cerebro-spinal fluid is always clear and colourless, and no coagulum forms on standing. During the acute stage, that is during the first two weeks, the average is - total proteins 0.03%, sugar normal, chlorides 0.72%, and cells 30 per cmm. (all lymphocytes with an occasional plasma cell). During the sub-acute or chronic stage the average is - total protein 0.02%, sugar normal, chlorides 0.752% and cells 3 per cmm (all lymphocytes). An increase of total protein occurs in 20% in the acute stage and in 7% in the subacute or chronic stage, and of cells in 100% in the acute stage and in 15% in the subacute or chronic stage. This "dissociation cyto-albuminique" is of value in diagnosis. During the acute stages, therefore, there are (1) A pleocytosis which varies in direct ratio to the severity of the disease, (2) A small increase of total protein not keeping pace with the pleocytosis, and (3) The cells present are all lymphocytes with an occasional plasma cell, and during the subacute or chronic stages the cerebro-spinal fluid is practically normal except for an inconstant small increase of cells, protein, and especially chlorides. In tuberculous meningitis

the sugar and chlorides are diminished, the protein and cells are increased and the cells present are mostly lymphocytes with a few plasma cells, polynuclear cells, and large endothelial cells. In encephalitis lethargica Stallybrass⁸⁶ has not found a sugar content of the cerebro-spinal fluid below 68 mgs per 100 cmm, while in tuberculous meningitis it is always below 60 mgs. per cmm. In cases of cerebral tumour the cerebro-spinal fluid is usually normal. In septic meningitis sugar is greatly diminished and chlorides are less than normal, while the cells which are mostly polynuclear leucocytes are increased enormously, making the cerebro-spinal fluid amount almost to pus. In poliomyelitis the pressure is increased, the fluid is clear, clots on standing (Perdrau⁷⁸), and the protein and cells are both increased, the latter being chiefly lymphocytes with a few polynuclears and may be as many as 1000 per cmm. (Vaidya⁸⁹). The increase of protein frequently occurs without a concomitant pleocytosis which is the reverse of what obtains in encephalitis lethargica.

Shiskin³³ in an examination of 23 juvenile cases of encephalitis lethargica found no marked changes in the pressure, colour, sugar content, cytology, or bacteriology of the cerebro-spinal fluid. The Wassermann was always negative.

Lange's colloidal gold test was performed in 20 cases and a luetic type of reaction was obtained in 16. A positive Lange reaction only occurred when globulin was present and she suggests that the reaction depends on a combination of the globulin and a toxin and that the aetiological factor may be of the nature of a spirochaete.

The examination of the cerebro-spinal fluid is not always decisive but Buzzard¹⁵ considers the following features to be suggestive. The fluid is under increased pressure and may be blood-tinged. A slight increase in cells, the majority of which are small lymphocytes, especially in the first few weeks after the onset of symptoms. A normal protein content even when considerable lymphocytosis. A moderate increase in glucose content, and a luetic curve with the Lange reaction in perhaps half the cases. The Wassermann is of course negative. Examination of the cerebro-spinal fluid was not performed in any of my cases as it was unnecessary.

Trophic symptoms sometimes occur. Bedsores are not uncommon especially in cases associated with incontinence as in my case 12. Sloughing bedsores occurred in one of Gullan's⁴¹ cases and pressure erythema in two others, while another case had septic sores of an intractable form on the fingers.

Cases simulating myasthenia gravis have been recorded. Hall⁴² saw a boy of 15 whose facies⁴¹ suggested this disease and two of Gullan's cases were of this nature. Extreme general muscular weakness and atrophy with ophthalmoplegia and exaggerated deep reflexes were observed in three cases by Grossman⁴⁰. The diagnosis of encephalitis lethargica was confirmed post mortem in one of them. A certain number of cases have been recorded in which bilateral parotitis was an early symptom. Hall⁴⁴ saw such a case in 1919. Early sialorrhoea is occasionally seen as in my case 1. Skin eruptions occur in a considerable number of cases but are not constant or characteristic. A diffuse erythema is the most common but purpuric, morbilliform, or scarlatiniform rashes may occur. They appear early, during the pyrexial period, and are very transient,³⁰ fading as a rule in twenty-four hours. Edgeworth saw three cases with urticarial, macular, or papular eruptions, and Bramwell⁵ occasionally observed a diffuse erythema. MacNalty⁵⁸ saw eruptions in 22 cases - a diffuse erythema in 13, slight papular in 3, slight petechial in 2, morbilliform in 2, and scarlatiniform in 2.¹² Buzzard and Greenfield's cases 1 and 3 had morbilliform rashes and case 2 had a scarlatiniform rash.

Disturbances of the liver have occurred frequently and Nonne⁸⁰ considers them to be due to a lesion of the brain centre regulating its functions. Polyuria has occurred in a considerable number of cases. It usually begins from the third to the seventh week somewhat suddenly, and often ends as suddenly. As much as 19 litres per diem may be passed.

DIAGNOSIS.

Careful detailed history taking is the first and most valuable asset in arriving at an accurate and early diagnosis. Any function of the brain or spinal cord may be disturbed, and therefore diagnosis does not depend on the presence or absence of any particular physical sign or symptom. Certain types are so common and characteristic that little difficulty attends their detection, but large numbers require very careful investigation before their true nature can be determined. Diagnosis depends on the recognition of an inflammation affecting larger or smaller areas of the brain, and exclusion, as far as possible, of other inflammatory or toxic lesions. Recognition of an inflammatory process is not always easy, but a detailed history of the onset and course is of the greatest assistance, while very useful information may be obtained from skilled investigation.

of the cerebro-spinal fluid (Buzzard¹⁵). Bramwell⁶ emphasizes the following points in arriving at a diagnosis of encephalitis lethargica. The history of onset especially such prodromal symptoms as drowsiness, diplopia, dim vision, or pains, and febrile disturbance with such associated general symptoms as headache, giddiness, delirium, dry mouth, and constipation. The presence of certain symptoms and signs with features dependent on the nature of the pathological process as much as on the anatomical distribution, and the exclusion of any other affection simulated. Ophthalmoplegia of central origin and more or less acute onset when present is almost distinctive. Other important diagnostic symptoms and signs are transient diplopia at the onset lasting a few days, nystagmus, irregular flickering movements, varying in rapidity, amplitude, and direction, on any attempt to move the eyes, paralysis of conjugate upward movement of the eyes, drowsiness and lethargy of varying degree, the mask-like face, initial mental dis-orientation, involuntary movements - myoclonic, athetoid, or choreic. But Edgeworth³⁰ considers that in the absence of lethargy no cranial nerve paralysis can be regarded as evidence of the presence of encephalitis lethargica. Other important symptoms which suggest its presence are an acutely

developing Parkinsonism, a cataleptic state, pupillary disturbances, violent neuralgia, a polio-myelitic syndrome, a peculiar delirium, a psychotic state, and signs of meningeal irritation at epidemic periods of encephalitis lethargica (Gullan⁴¹). As⁸³ has been mentioned Reynolds⁸³ emphasizes the foul tongue as an important point in diagnosis. In spite of the many clinical types, there is a marked tendency for a repetition of certain characteristic types and one type usually predominates during any particular epidemic. Thus in 1919 and 1920 the oculo-lethargic and amyostatic type occurred, while in 1923 the cases were definitely hyperkinetic.

The differential diagnosis from the large number of conditions which may, at one time or another, be simulated is not easy. An abrupt onset may simulate cerebral haemorrhage, haemorrhagic pachy-meningitis, and especially cerebral thrombosis. Two of Gullan's⁴¹ cases simulated apoplexy and one a haemorrhage into the pons. A detailed history of the onset is of especial importance in these cases. Mild cases with insignificant nervous symptoms may be mistaken for influenza, typhoid fever, or pneumonia, and the acute stage may be quite indistinguishable from influenza and only the residua give the clue to the diagnosis. Crowle⁵⁴ saw a girl of 17 who

was considered at first to suffer from either a peculiar form of influenza or hysteria, and a case²⁸ seen on November 13th 1920 by Denyer and Morley seemed to be suffering from a mild influenza with⁹³ no special symptoms. Weber saw a man of 23 with a "severe cold", which appeared to be a mild attack of influenza, followed a week later by drowsiness which lasted for five weeks. Six months later Parkinsonism developed. One of my cases simulated influenza.

Case 6, female, aet. 18, yarn examiner. In March 1924 she was "out of sorts" for some days and had to give up her work. When seen she had been in bed for two days and had slept most of the time. She was very drowsy, but could be easily wakened and complained of seeing things double. No ocular paralysis could be made out, and no facial paresis was present. The temperature was 102° , pulse rapid, tongue coated, and there was slight pharyngitis and cough. Next day she was much better and was up the following day and back at work in about a week. No previous illness. No residua so far.

This case I consider as one of encephalitis lethargica of the mild or abortive type. It occurred at the time when by far the biggest epidemic of encephalitis lethargica that has so far occurred in England was raging, and there was at the time practically no influenza occurring in the

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district. Gullan has found the headache of encephalitis lethargica not uncommonly occipital while that of influenza is usually frontal. Careful study of the temperature, examinations of the spleen, the appearance of the characteristic eruption, and a positive Widal will exclude cases of typhoid fever.

During the febrile stage perhaps the most difficult are the cases which simulate tuberculous meningitis. Examination of the chest for phthisis, and of the eyes for tubercles in the choroid may settle the question, while frequent convulsions indicate a meningitic rather than an encephalitic lesion. The most important and useful source of information is the cerebro-spinal fluid. The presence of the B. Tuberculosis in this is conclusive but in doubtful cases the sugar content, as has been mentioned is very useful. In two cases wrongly diagnosed as encephalitis lethargica it was 43 mgs per 100 ccm, and "much reduced" respectively (Stallybrass⁸⁶). The meningitic type simulates cerebro-spinal fever very closely; five of Gullan's⁴¹ cases were of this nature. Head retraction is usually more marked in cerebro-spinal fever, and tonic and clonic spasms occur, while the short duration of the acute illness, persistent vomiting, optic neuritis, an irregular temperature, and

meningococci in the cerebro-spinal fluid may, any of them, help to distinguish between the two diseases. Examination of the cerebro-spinal fluid is again of great importance. Septic meningitis, cerebral irritation, or an abscess of a "^{BLIND}fluid-area" of the brain may give trouble in some cases and are distinguished by the history of injury or ear trouble.

Quite a number of cases have simulated cerebral tumour and Bramwell⁶ considers this the most potent source of error. The difficulty is realised when one considers Buzzard and Greenfield's¹² cases 17, 18 and 20. The fact that a decompression operation was performed on case 19 speaks for itself. The history, examination of the discs, and a Wassermann examination of the cerebro-spinal fluid should serve to exclude cerebral syphilis. Paralysis agitans may be so closely simulated that the history alone will differentiate between them, but paralysis agitans is very rare under forty. Disseminated sclerosis is occasionally a source of difficulty, and tabes may be suggested in the later stages when the pupils are sluggish and the knee-jerks absent. A number of cases have presented symptoms of myasthenia gravis, and Grossman⁴⁰ who reported three such cases considered that if they had not occurred during an epidemic of encephalitis lethargica they would most

likely have been diagnosed as myasthenia gravis but the acute onset, the ages of the patients, the presence of ophthalmoplegia, and the absence of true myasthenic reaction in the muscles excluded it. Two of Gullan's⁴¹ cases also were of this type, and he found most difficult a case simulating progressive bulbar paralysis, but the absence of atrophy of the tongue, some improvement in the dysphagia, and paresis of the facial muscles confirmed the diagnosis of encephalitis lethargica. In rare cases catalepsy or epidemic stupor, hysteria, or neurasthenia may have to be excluded. Chorea gravis is sometimes simulated except that the movements^{PERSIST} during sleep (Stallybrass⁸⁶). Gullan⁴¹ saw one such case, and myoclonic and choreiform twitchings simulating chorea were the first symptoms in a girl of nineteen described by Weber⁹³; this was followed by lethargy and death. Some cases have resembled acute alcoholism, delirium tremens, acute psychoses, and acute dementia, while a case of Crowle's⁵⁴, a girl of twenty-one, was supposed to have dementia praecox.

A history of renal disease, oedema, and albumen and casts in the urine, will serve to exclude cases of uraemia. In two pregnant women reported upon by Herd⁴⁹ the onset was indistinguishable from eclampsia. Very rarely diphtheritic paralysis may

suggest encephalitis lethargica when a history of recent diphtheria and Klebs-Löffler's bacilli in cultures from the throat will make the diagnosis clear. Hall's ⁴³ case resembling an "acute abdomen" has been mentioned. Lastly botulism may be excluded by the absence of any source of food-poisoning and failure to isolate the bacillus botulinus from the food.

PROGNOSIS.

The average mortality being about 25% the prognosis as regards life is always grave. Of 135 fatal cases in which the exact dates of onset and death are given the percentages of deaths in each of the first four weeks respectively were 15, 34, 15, 13 (Hall⁴⁴), so that the second week is the most fatal period and if the patient survives the third week the prognosis as regards life is considerably better. Sudden death is not uncommon especially when the medullary region is involved.

Several factors appear to add to the gravity of the prognosis in different cases. A sudden onset is considered by some to be more serious than a gradual onset, and Gullan⁴¹ considers cases simulating cerebral haemorrhage to be the most grave.

Severity of onset, however, is no guide to prognosis, one case with violent mania recovered completely. Lethargy which begins gradually, and deepens day by day, is of serious import, especially if accompanied by rising temperature, profuse sweating, and incontinence (Bramwell⁵). The prognosis in cases of the excito-motor type is very uncertain. When the myoclonic cases were first observed in 1919 and 1920 by Boveri⁴, Ellis³¹, and others the mortality amongst them was very high, but since then similar cases of less severity have been common and the gravity of this type as regards life is not as serious as was at first thought. Still Gullan⁴¹ writing in 1925 states that the hyperkinetic cases are more virulent than the somnolent-ophthalmic or amyostatic. Parsons⁷⁸ found that cases with general symptoms without localising signs, type 1, were more fatal than other types. Early stuporose lethargy in young children with signs of meningeal irritation are of serious import (Hall⁴⁴). However, these various opinions are not of much consequence and only serve to indicate the specially grave features. The prognosis as regards life is very uncertain, and must be most guarded in every case.

Of almost greater importance, however, in the majority of cases, is the question of prognosis as regards complete recovery. It is the frequent occurrence of recrudescences and residua in cases of encephalitis lethargica that make it the serious disease it is.

Recrudescences occur very frequently, usually during epidemic periods, but any patient may have a recrudescence, which may prove fatal, at any time after the primary illness, and two or more relapses are not uncommon.

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Buzzard defines sequelae as 1. Disorders of function which appear for the first time after the disease has spent itself (e.g. Epilepsy), and 2. Progressive alterations in defects of function which have been left as more or less permanent legacies of the disease (e.g. Parkinsonism). ~~The~~ The first of these might be called "sequelae", and the second "residua", but as it is known that the disease may be latent for long periods and then give rise to symptoms of chronic inflammation, I think it is better to group all the after-effects under the heading of "residua".

Residua may follow the slightest attack
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of encephalitis lethargica. Symonds found that only a small proportion of cases with residua had

~~had~~ been diagnosed during the acute illness, and
 hardly any of Reynold's ⁸³ cases of Parkinsonism
 had been diagnosed as encephalitis until the
 Parkinsonism developed, and many not even then,
 being sent to him as cases of neurasthenia. Of
 Gullan's ⁴¹ cases the complete recoveries up to date
 were 50%, but Cruchet (Paterson and Spence ⁸¹)
 reviewing the results of 32 cases states that 12
 were fatal and all the others have residua, while
 Nonne ⁸⁰ goes so far as to say that few cases are
 definitely cured and after-effects are more or less ⁸¹
 marked in nearly every case. Paterson and Spence
 reported the disease in 25 children, only one of
 which ~~died~~ⁱ, and only six of the remainder made a
 complete recovery. They found residua to be more
 severe in young children, of those under one year
 only one made a complete recovery and four are
 mental deficient. A severe acute stage in a
 young child seems to favour the occurrence of residua,
 if lethargy lasts three or four weeks some mental
 deficiency must be expected, a short illness with
 lethargy for only a few days usually results in
 complete recovery.

The most common and most serious residuum is the condition known as Parkinsonism, and speaking very roughly one may say that 25% of cases are fatal, 25% make a complete recovery, 25% develop Parkinsonism, and 25% suffer from other residua. Parkinsonism may be early or late. Early Parkinsonism has been mentioned as a symptom of the acute illness, it may persist for some months but as a rule it slowly improves and eventually disappears altogether. Late Parkinsonism is essentially the same condition, but it appears after the initial stage is past. It may follow any type of encephalitis lethargica. Weber⁹³ was the first to report its occurrence after an ambulatory attack with drowsiness. My case 7 is of this nature. The most common time of onset is six to twelve months after the acute attack. Occasionally the interval is longer, and cases have been recorded in which it has been five, six or even seven years. Complete recovery between the primary illness and the development of Parkinsonism is rare, in most cases the recovery is incomplete and the patient is easily tired, dull, and shows a complete lack of interest and initiative. In 1919 Wilson⁹⁵ reported two of the earliest cases of Parkinsonism coming on during convalescence, and Buzzard and Greenfield¹² saw a

case in December 1918 followed by Parkinsonism. The development of Parkinsonism is very frequently insidious, and it is often difficult to fix the exact time of onset. In many cases it is not recognised for some time. Hall⁴⁶ reports a case in which there was definite slowness of action for two years before the alleged onset of Parkinsonism, and the patient was dismissed from his employment because of it eighteen months before the characteristic signs appeared.

Case 7, female, aet. 20, stenographer. From July 1924 to April 1925 a period of nine months, she suffered from very severe and persistent insomnia, but was otherwise in good health, and doing her work all the time. In April 1925 she had a slight sore throat for a short time, and from then until February 1926 she complained of tiredness, weakness and lassitude. She slept much better but talked and sometimes sang in her sleep, when she woke up she did not know she had been doing it. During this time she occasionally felt very sleepy in the day time, but never actually went to sleep. In March 1926 typical Parkinsonism was observed for the first time. She walked well, spoke normally, held her head up as in health, but she had the typical attitude of the arms. Her mother stated that she had not changed in character, but was not as lively as she used to be

she was listless, languid, never wanting to go out or do anything, always complaining of being tired, and that she had got much thinner. On examination there was no tremor of the limbs while at rest, but sustained movements developed a tremor of about five to the second. Rombergism was absent but she tended to move backwards when standing. There was a slight extra-pyramidal increase of muscle tone in all four limbs especially affecting the left side. Voluntary muscular power was less than normal, and there was a very slight weakness of the left side of the face for emotional movements. The tongue was coated and saliva excessive. She had been working throughout her illness, but was ordered rest and change of air. She returned to work after being absent a month with the condition unchanged and has worked continuously up to a month ago when she had to give up, although her condition was apparently unaltered. Arrangements are now in progress for her admission to hospital for a course of massage and rest. She had been having tinct. belladonna since March up to date (August), but it has not had any effect on her condition.

Of considerable importance from the point of view of compensation is the fact that in a number of cases Parkinsonism has developed soon after an

injury. If trauma plays a part, it is probably that of unmasking a latent Parkinsonian and precipitating its onset. In this connection observations have recently been made on cases following vaccination.

The general features consist of an increase of muscle tone leading to characteristic unnatural postures of the head, trunk and arms. ²⁷ Davis reports the case of a young woman with encephalitis lethargica during pregnancy followed by Parkinsonism, who had tonic contraction of the arms with the elbows flexed across the chest. Under an anaesthetic the arms were extended and put up in plaster. After three weeks the plaster was removed and it was then found impossible to flex the arms. The face is mask-like and immobile, in some cases there is a spastic smile. The head is held stiffly erect, or more commonly the shoulders are rounded and the head bent forward. When the arms are affected they are carried semiflexed and across the front of the body in the paralysis agitans attitude, and the fingers may be in the accoucheur's position. The following is an illustrative case.

Case 8, male, aet. 22, joiner. In January 1924 he had a mild attack of what was apparently influenza with very severe headache and sleepiness. He had no cranial nerve lesion, but was confined to

bed for six weeks. The convalescence from this was protracted and though he started work again he had to give it up owing to weakness of the legs and pains in the back. The weakness continued but did not get any worse nor improve up to April 1925, but he worked on and off during this time, as long as five months at a time. He had two attacks of "influenza" between January 1924 and May 1925, but the exact dates of these are unknown. In September 1924 he vomited every morning on rising for a few weeks. He had been much more talkative at home since the first illness and in March 1924 he talked until 2 a.m. on several nights. Examined in April 1925, he complained of weakness of the right arm and both legs, and trembling of both arms and legs when cold, and that he stooped a great deal in walking. He had a mask-like vacant expression of face and walked with his head bent forward, but the gait was normal. The right arm was carried slightly flexed, the hand preferably in the coat pocket, and there was a fine rhythmic tremor of the arm. The teeth were healthy and the tongue clean. The heart, lungs, and abdomen were normal, there was no spasticity of the abdominal muscles or alteration of the reflexes. The knee-jerks were normal, the right slightly greater than

the left. The plantar reflexes were sluggish, the right extensor and the left flexor. The right tendo-achilles jerk was brisk, and there was slight spacticity of both legs. There was slight nystagmus to the right, the cranial nerves were otherwise normal. The right grip was slightly feebler than the left. In May 1925 he had an acute attack of influenza and pneumonia. He could not work from that time until January 1926 owing to weakness, and inability to work fast enough. In November 1925 he had six weeks at a convalescent home which did him a lot of good. Seen in February 1926, he had been working full time as a joiner for five weeks. He complained of severe salivation and stated that this had been troublesome for about twelve months, the saliva escaped from the mouth at times. Before his illness he was always quiet at home but cheerful with his pals; since January 1924 he had been much more talkative at home and brighter mentally with more to say. At one period he was very depressed and almost suicidal. On examination the gait was normal, but he carried his head bent forward and the arms semiflexed especially the right. The face was mask-like, but a broad grin appeared if he saw he was being looked at. Diplopia was complained of on looking upwards or to the left; there was no other ocular lesion. The teeth were good; there was slight pyorrhoea; the tongue was clean. There was a slight

pharyngitis. The reflexes were normal and so were the heart and other organs. He had a small simple goitre. The arms and legs, especially the right, trembled when cold, and there was a fine rhythmic tremor of the right arm. He sat in a characteristic attitude with the arms flexed, the hands half-closed and their ulnar borders resting on the knees, and the head bent forward. In May 1926 he had been on belladonna for some time but the condition remained unchanged. He had to stop work again owing to slowness. In July 1926 he was still off work and remained the same.

In most cases there is slight tremor, but in some it is severe, while in others it is practically absent. The voice is as a rule slow and monotonous, and it may be slurring, but in some cases it is very rapid and almost unintelligible. Sialorrhoea is a striking and often early symptom, the saliva requires frequent efforts to swallow it and may even escape from the angles of the mouth. The pulse rate is usually increased and in ambulatory cases is often persistently over 100 per minute.

The most characteristic feature is the extreme slowness of action, which may be limited to one part or generalised. When it affects one hand only this is noticed by the patient as being slower

than the other; a musician and a typist both complained that the right hand could not keep pace with the left. But when both arms are affected the slowness is not usually noticed by the patient who believes he is as quick at his work as ever. The slowness shows itself especially in ordinary everyday actions such as dressing, washing, feeding, and putting on the boots. In generalised cases the rate of movement may be as much as ten times slower than normal. Muscular power eventually fails in most cases but may remain very good for a long time. Some patients are depressed, melancholic, and suicidal, some are apathetic, others appear to have a pathological optimism, always "better" even with no improvement. Some cases show "kinesia paradoxa", a momentary alertness and agility in patients whose habitual slowness is extreme. Hall⁴⁶ reports the case of a boy who after bathing in the sea sprinted along the beach to his mother as well as ever he did, only to resume his usual Parkinsonian state when he reached her. The festinant gait with either propulsion or retropulsion is very common and is a feature of three of my cases. Micrographia occurs in some cases. The rigid mask-like face, slow speech, dribbling of saliva, and anthropoid gait are very characteristic if not pathognomonic and often enable a diagnosis to be made retrospectively.

The prognosis of cases of Parkinsonism is very difficult to determine accurately. Some cases progress very rapidly and end fatally within six months or a year of the onset of Parkinsonism, others have died after a longer period. In others it progresses until the patients are helpless and require constant attention and then appears to become stationary. My case 12 is of this nature. A number of cases do not develop to the severe and crippling phase, but remain stationary for a very long period.

Case 9, male, aet. 37, brass turner. In March 1918 when he was 29 he developed a trembling of the arms and legs, severe pain and stiffness of the back of the neck, drowsiness and lack of interest in anything. He kept going about for a week and then had to take to his bed where he remained for four months. He was so severely asthenic that he could not lift a limb and had to be fed; he also suffered from aphasia. In July 1918 he was sufficiently recovered to spend three weeks at a convalescent home and when he returned home he developed twitching movements of both shoulders and of the jaw of a jerky choreic nature, which persisted for three months. In October 1918 he was well enough to start his work again, the only disability being a slight tremor of the legs, and he continued at his

work until June 1920 when he had to give up owing to tremors of both arms and legs. He has not worked since. In March 1924 he first noticed a tendency to scrape the right toe on the ground in walking and this has been present ever since. In March 1925 propulsion first made its appearance and has persisted. Apart from these two fresh developments his condition has remained practically stationary since 1920. In March 1926 he had a slight attack of influenza with malaise, pains in the limbs, catarrhal symptoms, and occipital cephalgia, but was not confined to bed. Since 1918 his character has changed somewhat; before he was bright and cheerful and an enthusiastic gymnast, cricketer, and footballer; he has become very quiet, depressed and is rather irritable at times. He has never been confined to bed since 1918. Examined in May 1926 he sat with his head bent forward, his elbows flexed and his hands half-closed and resting on his knees. There was a fine rhythmical tremor of the arms and legs. In walking he dragged the right toe along the ground and tended to fall forwards, walking with his head bent forward and his shoulders rounded. In standing or walking he kept his arms semiflexed at the elbows and his hands in front of him. When he spoke his features remained immobile and he talked

with his lips only. The articulation was slow, very indistinct slurring, and in a monotone. Temperature was normal, pulse 96, and the tongue clean and tremulous. The pupils reacted and were normal, there was loss of convergence of the eyes. Smiling was normal, but on attempting to frown, which he could not do, his upper eyelids flickered rapidly up and down. The knee-jerks were both exaggerated, the right more so than the left, and there was ankle-clonus and Babinski's sign of the right foot. He was put on belladonna treatment. In June 1926 he had been on belladonna for a month and showed much improvement especially in his mental outlook, being much brighter and more interested in things and not so irritable. He said he felt much better and had not such a great tendency to fall as before. He was getting out more and could walk better than he had done for years. In July the improvement was still continuing.

This case is of special interest because it is one of the earliest cases in England and shows that Parkinsonism may remain practically stationary for six years or more. Some cases gradually improve and recover apparently completely; this

occurred in 50% of Gullan's⁴¹ cases. Periods of improvement to a surprising extent occur in some cases and sometimes last for a considerable time. When Parkinsonism develops slowly, some time after the acute attack in a young person the prognosis is very bad (Feiling³²).

Parkinsonism is distinguished from paralysis agitans firstly by the age of the patient. Paralysis agitans is very rare under forty, while Parkinsonism is quite common in young people. The typical pill-rolling tremor of the hands of paralysis agitans is usually absent in Parkinsonism, in the latter the rigidity is often earlier and more troublesome and remains "fragmentary", that is confined to certain parts, longer than occurs in paralysis agitans. Parkinsonism is frequently associated with other residua such as muscular movements, ophthalmoplegia, mental or moral changes and these help to distinguish it from paralysis agitans. The mask-like face develops slowly and late in paralysis agitans, while in Parkinsonism it is early and often rapid in appearance.

Mental residua occur very frequently, especially in children and young adults. The defect may be only slight (As in the four school-girls with mental deterioration and fits of laughing and crying reported by Fyfe³⁶ .) or very severe amounting to

gross mental deficiency for which the patient has to be sent to a mental asylum. Of 25 children reported⁸¹ on by Paterson and Spence seven are gross and eleven minor mental deficient. The former are permanent and hopeless idiots, and of the latter some are imbeciles and incapable of earning a living while others are only backward and dull. Some cases show symptoms of nervous exhaustion such as lack of energy, concentration, and decision; as well as depression, restlessness, irritability, and insomnia.¹⁸ Collier reports a girl of twenty who had frontal headache followed by strabismus, somnolence, complete lack of initiative and retention of urine. The condition has remained unchanged, she never moves or speaks unless told to, and requires daily catheterisation. Buzzard¹⁴ saw a case of delusional insanity, lasting two weeks, two months after an attack of encephalitis lethargica. Maniacal outbursts, homicidal and suicidal attacks, and psychoses such as dementia praecox have been recorded. In 1923⁴⁴ Hall circularised the asylums in England and Wales and found that only 30 mental cases as a result of encephalitis lethargica had been certified up to then.

Moral changes without any actual mental deterioration are of very frequent occurrence. These may take the form of lack of self control, lying, theft, or changes in temper and character.

A well behaved child becomes mischievous and untrustworthy. Batten and Still³ in 1918 reported four cases of the disease in young children under the name "epidemic stupor". Their ages ranged between three and a half months and eleven years; all were of an oculo-lethargic type with recovery and Parkinsonism followed in one case. Of these four cases it is interesting to note that one, quite mentally deficient and incapable of recognising even her own parents, is now an inmate of a mental hospital, one has become a dull, backward and slow-witted child, and another is now an incorrigible kleptomaniac and has spent most of the period since recovery under detention for theft (Paterson and Spence⁸¹). Some become dirty in their habits; this was noted especially by Findlay³³ in his cases, and Poynton⁵⁴ reports a number of moral imbeciles who are all now in asylums. Gullan⁴¹ saw two cases with loss of affection for their parents, and four cases with changes of character, two are lazy, one is rude, and one is irritable, and he reports boy with change of character for a year who has become normal. He considers that some of the mental changes considered as residua are due to too lenient treatment in convalescence, while Cameron⁵⁴ found that the abnormality of conduct did not differ in type from that which results from faulty parental management:

it amounted to a manifestation of the strong desire to cause a sensation and attract attention, and Shrubshall⁵⁴ is of opinion that the application of educational methods early would obviate many of these children being sent to asylums. Many cases are beyond parental control, while quite a number have reached the police courts and given rise to a very important medico-legal problem.

Nocturnal restlessness and excitement has been very frequently observed in children. It appears to be a manifestation which occurs in the stage of recovery from the acute symptoms and is not permanent, lasting months or years, but passing off gradually in time. Fletcher³⁴ reported two such boys with apparent complete recovery. In some cases it is the only symptom of the disease for a considerable period as in my case 5. Towards evening the child becomes restless and excitable, this becomes worse at bed time, and the whole night is spent in ceaseless activity, talking, singing, whistling, moving about in bed or getting out and running about. When the morning is well advanced the child falls into a heavy sleep which may continue until mid-day. On waking there is no excitement and the child appears quite normal until evening approaches. Hofstadt³⁴ (Rolleston) records 21 children who for weeks or months were in a state of constant restlessness

during the night and unable to get to sleep before five or six in the morning, but were normal during the day. Findlay³³ found that lethargy for varying periods was in many cases followed by night restlessness, and this had been a typical and striking feature of his cases. They spent the night shaking the pillows, arranging the bed, muttering and singing. They might even get up in the middle of the night, dress themselves, and go out into the streets to play! During the day the drowsiness was slight or absent. Findlay and Shiskin (Rolleston³⁴) regard nocturnal restlessness as the most characteristic feature of encephalitis letargica next to choreiform movements. In the majority of cases the diurnal somnolence is slight but some patients sleep all day. Three of my cases had marked nocturnal restlessness, case 5, and the two following which are very similar in many respects.

Case 10, male, aet. 9, school-boy. In March 1924 he began to be restless at night and drowsy in the day time. This gradually got worse; he spent the whole night shouting and singing and wriggling about in bed so that in a very short time he wore through many sheets by the constant rubbing.

While so restless at night he slept all day, without food, having his first meal at 10 p.m. When seen in April 1924 he complained of occasional headaches and pain in the left side. He had never had convulsions or fits. Appetite was good and bowels regular. Previous health good. On examination there were no abnormal physical signs except enlarged tonsils, and the urine was normal. Seen on May 2nd 1924, he was still drowsy by day and restless at night, but did not attempt to get out of bed. He was very easily excited. He had slept from 6 a.m. to 4 p.m. the previous day, but had been wakeful throughout the whole of the last night. He was in hospital for observation from May 6th to May 18th 1924 and while there was restless at night and slept during the day, and he complained of a sensation as though his legs were dropping off at night. No strabismus, nor diplopia, nor paralysis or paresis of any other cranial nerves. Knee-jerks exaggerated. No Parkinsonism. Plantar reflexes normal. Respirations 24, no sphincter trouble. Between July and October 1924 he improved gradually and was sleeping fairly well at night. In August 1925 he began to fall down on his back when outside, but never fell in the house. The falls quickly became more frequent and a thing of common occurrence. On February 11th 1926

he had been noisy and restless three nights during the previous week, but otherwise had slept well at night for some time and was bright and cheerful during the day time. He was always smiling and seemed very easily amused. He spent most of his time outside and shouted, laughed and pointed at everyone who passed. He was going to school every day and as he could not walk far without falling he was always carried to and from school by two of the bigger boys who had promised to look after him. He could not walk more than a hundred yards without falling down backwards, that is to say he always landed on his back. His left side, arm and leg, were paresed and he had a tendency to fall towards the left side so that he had worn holes in his clothes on the left shoulder by rubbing it along walls when walking, and he had worn the toe out of his left boot by dragging it along the ground. When he came into the house he was in the habit of leaning against the wall just inside the door. He would then slowly slip down the wall until he was eventually lying on his back on the floor. The wall paper at the door was all worn away with the constant friction. He could only stand for a few seconds before he began to move backwards and continued to do so until he either leant against something or fell on his back. When he walked forward his gait was quite normal except for a

dragging of the left foot, but as he continued he seemed to overstep his balance and gradually leant further and further backwards until he lost his balance and sat down. When he sat on a chair he gradually slid down until he was lying full length on the chair. In walking, the arms were carried at the sides as normally and the head fairly erect. Indoors he was always fighting with his young brother, swore a great deal, cried easily, and was always spitting about the house. At meals he could not use a knife and fork as he kept dropping his food when he did so, so he always used his fingers. On examination there were no abnormal physical signs except a slight hemiplegia of the left side. Previous illnesses consisted of meningitis at nine months old when he was ill for six months, and scarlet fever some years later. He was perfectly well for at least two years before the onset of this complaint.

Case 11, male, aet. 8, school-boy. In May 1924 he gradually became sleepless at nights and for some months he was acutely excited and noisy all night and drowsy in the day time. He also had trembling of all four limbs and a tendency to fall forwards when he walked. He had a slight squint at the onset and admitted seeing double. He improved very much in hospital and was well on the way to recovery when in December 1924 he had a

recrudescence and rapidly became worse and then remained stationary. On examination in March 1926 he was a small thin boy, but cheerful and amiable. He walked slowly and only with great difficulty and had a spastic gait with a tendency to fall backwards and to the right side. If he walked any distance he fell backwards. He fed himself but could not use a knife and fork and always used his fingers. His bowels were rather obstinate, appetite good, and tongue clean and moist. The temperature was normal and the heart and lungs healthy. The pupils and ocular movements were normal, no strabisms, nystagmus, nor ptosis. He slept well at night but was stupid and drowsy in the morning, becoming more wide awake later in the day. Both knee-jerks were exaggerated, the right more so than the left, and there was weakness and spasticity of both legs and the right arm. He tended to fall backwards and towards the right side.

Respiratory residua are common especially in children and affect only the nervous mechanism of breathing. Tachypnoea has been frequently noted. It occurs usually in periodic attacks and may be followed by prolonged apnoea during which the child becomes cyanosed. Cheyne-stokes breathing, spasmodic cough, respiratory tics, and abnormal

rhino-laryngeal sensations have been recorded.

Respirations of 80 per minute lasting for a fortnight⁸⁶ or more were seen in two cases by Stallybrass⁸⁶.

⁴¹Gullan saw three cases with marked dyspnoea. In one case the respirations were 70 - 80 per minute for eleven weeks, and in another 30 per minute for fourteen weeks; in these two cases rhythmic contractions of the muscles of the right arm and leg⁵⁰ occurred with each inspiration. Howell⁵⁰ saw a girl of twenty who, three months after encephalitis lethargica, had Cheyne-stokes respiration 36 per minute; and contraction of one platysma causing the mouth to open occurred with each respiration.

⁵⁴Cameron reports two cases with nocturnal restlessness in which attacks occurred of noisy breathing, flushed face, and puffing out of the cheeks.

Residual paralysis occur occasionally but their rarity is striking when compared to the results of acute poliomyelitis. Although flaccid paralysis sometimes occurs a spastic hemiplegia or diplegia with exaggerated reflexes and Babinski's sign is commoner. ⁵⁴Jewesbury⁵⁴, ⁵⁴Cameron⁵⁴, and Paterson and ⁸¹Spence⁸¹ have recorded such cases, and three of their cases had ataxia and incoordination of the arms. Ataxia of the arms and legs associated with hemiplegia has occurred in three of my cases

(cases 9, 10, and 11). Hall⁴³ recorded two cases of paraplegia which recovered. Any form of ophthalmoplegia may be left and the changes in the pupil which may persist are especially important because they may suggest Tabes or General paralysis of the insane. Severe optic neuritis occasionally occurs late in the disease. Attacks of drowsiness and headache sometimes recur from time to time after the acute illness is past.

An infinite variety of excito-motor residua have been recorded. These are not infrequently associated with Parkinsonism. The movements are involuntary and rhythmical in character; the rhythm sometimes bears a relation to respiration. They may be choreic, myoclonic, bradykinetic, or shaking in character. Myoclonic movements are ^{shock-like muscular spasms} sudden/affecting most commonly a limb, but the abdominal muscles, the diaphragm, and the larynx are not infrequently involved. Bradykinetic movements are described as large slow rhythmic global movements involving one or more limbs or the head and the trunk. The movements usually gradually improve but in some⁵⁴ they persist for years. Parkes Weber⁵⁴ showed

a case of bradykinesia resembling slow-motion cinema
 films. Abrahamson²⁷ saw a case with residual
 muscular movements of the arms which were slower
 than choreic movements, resembling intentional
 movements; they were slow, coordinate and asymmetrical.
 Buzzard and Greenfield's¹² case 14 had involuntary
 movements of the right toes spreading to the arm and
 leg and persisting, and case 15 had irregular rhythmic
 tremor of the trunk especially on the left side.
 Macbride⁵⁶ saw three cases resembling spasmodic
 torticollis. Buzzard¹⁴ reported a case with rhythmic
 muscular contractions corresponding to the pulse rate.
 Hiccough occurs frequently and may last many months.

Trophic residua such as marked obesity,
 sometimes accompanied by excessive sweating, loss of
 sexual power, and a female appearance have been
 recorded. The interest of these lies in their
 possible relation to hypophysis disorder, and the
 occurrence of polyuria and also lethargy (Hall⁴⁴).
 Howell²⁹ observed severe seborrhoea of the face and
 scalp in six cases. The patient sometimes develops
 an abnormally large appetite as in my case 5.

The morbid anatomy of the residua of
 encephalitis lethargica has not been very definitely
 established. In 1919 Buzzard and Greenfield¹²

described calcareous degeneration of the vessel walls and clots in the brain of a fatal case. In the basal ganglia there were very many calcified deposits in the walls and lumina of larger thrombosed vessels. Buzzard then suggested that late clinical complications might be due to secondary vascular disturbances. In 1923 Buzzard¹⁴ found hyaline and calcareous degeneration of vessel walls, involving chiefly the media and adventitia, in cases fatal early and late in the disease, and considers that this leads to interference with the nutrition of the nervous elements, due to unreliable blood supply, resulting in gradual loss of functional activity with symptoms of progressive deterioration. Cases with myoclonus corresponding in rhythm to the pulse rate are of interest in this connection. These changes affected especially the basal ganglia in cases of Parkinsonism. Other changes he found were a chronic and intermittent hydrocephalus, due to imperfect drainage of the ventricles, meningeal thickening, and occasionally loculated meningeal cysts interfering with venous drainage from the optic nerves. Symonds⁵⁴ saw a woman of 38 with severe fatal Parkinsonism who had perivascular "cuffs" and marked hyaline and calcareous degeneration of the small arterioles in the corpus

striatum, supporting Buzzard's view that the residua are due to progressive degenerative and obliterative changes in the vessels and consequent anaemia of the nervous tissue. ⁶⁵ Mc Alpine found calcification in the anterior part of the globus pallidus in both acute and chronic cases, and he also found it in cases of Huntingdon's chorea and paralysis agitans. He does not think that the calcification plays an important part in producing Parkinsonism because he found - 1. The lumina of the affected vessels were patent and there was no evidence of serious nutritional alterations in the cells in the neighbourhood. 2. In two cases with choreiform movements, but no rigidity, calcification was present in the globus pallidus. 3. In case 5, a chronic encephalitis with involuntary movements and slight Parkinsonism (which may have been accounted for by the changes in the substantia nigra) there was a more advanced degree of calcification in the globus pallidus than in any of the cases with severe Parkinsonism. The lesions of paralysis agitans are chiefly in the globus pallidus, but Tretiakoff ⁶⁵ (Mc Alpine) found lesions in the substantia nigra in nine cases of paralysis agitans and also in cases of Parkinsonism. In Mc Alpine's ⁶⁵ case 1. he found marked changes in the substantia nigra.

The pigmented cells were greatly reduced in number and their place was taken by scattered particles of pigment. The few remaining cells showed eccentric nuclei, extrusion of pigment, vacuolization and loss of normal processes. Macro- and microphages, of glial origin, were plentiful, many packed with pigment. They could be traced to the perivascular spaces. In the walls of the larger meningeal veins in the interpeduncular space were numerous particles of pigment, also in the lumina of the vessels usually inside macrophages. Perivascular infiltration was marked. A few vessels showed hyaline degeneration of their walls. Numerous recent haemorrhages were present especially in the ventral half of the mid-brain. He considers these changes to be the cause of Parkinsonism, but I think Buzzard's view is the more probable.

Mental residua are probably due to lesions of the cortex. Involuntary movements are difficult to explain. They may be due to irritative stimulation or unopposed activity, but as Buzzard¹⁴ points out artificial anaemia of the cortex produces involuntary clonic movements. Metabolic disturbances so often noted after an attack point to inflammation of the controlling brain-centres. Late optic neuritis is probably due to a local meningitis causing obstruction to the venous flux from the optic nerves.

Study of the pathology of encephalitis lethargica has given useful information as to the functions of the lenticular and candate nuclei, parts of the brain controlling voluntary innervation of single groups of muscles. The slightest conscious voluntary innervation of a given group of muscles requires an involuntary synergic innervation of numerous other muscles. Chronic encephalitis disturbs this innervation control. The muscle tone and the attitude and position of joints are regulated apart from conscious volition to a large extent in the ganglia which are chiefly affected by the inflammation of encephalitis lethargica (Nonne⁸⁰). The cerebellum also maintains muscular tone during rest, and coordinates muscular movements during activity. Its functions are of special importance in the maintenance of equilibrium and lesions of this part of the brain produce ataxia and defective muscle tone. Catalepsy, such as occurs in Parkinsonism, is believed to be due to a lesion of the ganglia between the optic thalamus, the corpora geniculata, and the pineal Body (Economo²⁹). This is of interest because "will" or "intention", formerly believed to be entirely the result of psychical processes, and its disturbance to be a

symptom of psychical disease, is now found to have an organic basis, its disturbance being associated with a lesion in the borderland between the ganglia connected with sensations and movements. This puts certain neuroses and psychoses, formerly believed to be entirely due to psychic processes, on a new anatomical basis.

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TREATMENT.

When an epidemic of encephalitis lethargica occurs in a district it is the duty of medical practitioners and the Medical Officer of Health to investigate any associated conditions which may throw light on the epidemiology, to keep an alert watch for mild or abortive cases, and to aid in any practicable pathological investigations and in obtaining material for the purpose.

The Public Health Authorities should distribute leaflets, put up posters, place notices in the press, show cinema films, and give lectures in the schools on how to guard against infection and what to do when it occurs. Information about any local facilities for treating patients which have been provided should be circulated to the public. All crowded assemblies should be discouraged and gatherings of children avoided. Young children must not enter a house where there is a case. Owing to the importance of good nursing in acute cases hospital treatment should be obtained wherever

possible and the isolation hospitals of local authorities should be available for this purpose. The Medical Officer of Health should also follow up the after histories of cases especially as regards mental residua.

Where hospital treatment is not obtainable the patient has to be treated in his own house and for such cases public nursing facilities of some kind should be available. The other occupants of a house in which a case of encephalitis lethargica is being treated should be assured that the risk of infection is very slight, but only those in actual attendance on the patient may enter the sick room. School children in the affected household should be kept away from school for three weeks after isolation of the patient as a precautionary measure. Attendants on the patient should use antiseptic nasal sprays or douches and gargle the throat. Any person in the house who suffers from sore throat or other symptoms suggestive of a mild attack should be treated and isolated as far as possible until recovered. As soon as the disease is recognised

the patient should be isolated from other members of the household. The sick room should be the largest bedroom with plenty of light; it should be well ventilated and warm, and all movable and unnecessary articles should be removed. It should be thoroughly cleansed and disinfected at the end of the illness. In severe cases the services of a trained nurse are almost essential and day and night attendance are required.

The patient should be confined to bed. This applies equally to the severe case or the mild case with only slight symptoms (Buzzard and Greenfield)¹²
⁴³ Hall appears to doubt the wisdom of putting a lethargic patient to bed suggesting that it may be so conducive to sleep that it only increases the stupor and causes the patient to lapse into a fatal coma. During the pyrexial period only liquid food should be given, and milk should be limited as it promotes constipation. Cold sponging is often beneficial and tends to diminish the delirium. Constipation is very obstinate and calomel, croton oil, or enemata may be necessary. Once the bowels have moved liquid paraffin or phenolphthalein are usually successful in securing a daily action. Great care must be taken to prevent bed-sores. The points of pressure should be bathed with spirit two or three times a day and powdered with zinc and starch powder. Daily cleansing of the mouth and

antiseptic treatment of the mouth, nose, and throat should be carried out. Retention of urine should be watched for as catheterisation is sometimes necessary. The lungs should be frequently examined for respiratory complications.

When delirium is violent the patient has to be nursed on a mattress on the floor. Dysphagia may require nasal feeding. In cases with partial ptosis the affected eye should be shaded to prevent the entrance of foreign bodies; cases with severe photophobia require the room darkened. Pain and tingling in the limbs due to polyneuritis is best treated by protecting the parts from the bed-clothes by means of suitable frames, and by the application of heat either by electricity or hot-water bottles.

Lumbar puncture is often beneficial especially when the fluid withdrawn is under increased pressure or symptoms of meningeal irritation are present. When improvement results lumbar puncture may be repeated at intervals according to the condition of the patient.

No specific cure has yet been discovered for encephalitis lethargica, but many drugs have been found of benefit in certain cases. The universal use of large and repeated doses of hexamine

is strongly to be discouraged on the grounds that in a number of cases the urine has become loaded with albumen and blood, and the condition does not clear until the drug is discontinued. During the exhibition of hexamine the urine must be examined daily. Bramwell⁶ has given it in doses of ten grains every four hours, but has had no definite proof that it is of any value. Denyer and Morley²⁸ report their results of intravenous hexamine in one case. Marked improvement followed the injection of gr 10, and next day gr 20 was injected with still more improvement. The patient died four days later.

⁵ Bramwell recommends strychnine hypodermically in large doses up to half a grain, and has also found quinine beneficial. Gullan⁴¹ advises sodium salicylate gr. 15 - 30 every three or four hours, and where there is restlessness and insomnia he has had satisfactory results from gr. 5 - 10 each of potassium bromide and potassium iodide. Luminal gr i or gr ii at bed time is very useful for insomnia, but in severe cases an intramuscular injection of one or two ccms of boiled milk has produced wonderful results; my experience of medinal has been very disappointing. Economo²⁹ obtained good general results, in acute cases, from larger doses of intravenous iodine. Netter (Bramwell⁶) has employed intrathecal injections of convalescents' serum with

possible benefit, but considers it premature to recommend this procedure. He recommends the production of a fixation abscess in the thigh by hypodermic injection of turpentine. Of 19 cases so treated only 2 died, while of 25 cases not treated in this way 13 died.

During convalescence a course of massage combined with hot baths and electrical treatment is usually advisable. Patients should be warned that they will probably not regain their full strength for at least six months after the illness, and should be examined at intervals for evidence of residua.

In the later stages, in cases with mental residua, especially in children, and in severe cases of Parkinsonism the question of institutional treatment again arises. Some cases can be certified under the Mental Deficiency Act 1913 as moral imbeciles, while others who are only "difficult" or "impossible" or are beyond parental control require institutional treatment almost as much (Auden ²). In London and Lancashire patients suffering from mental after-effects of encephalitis lethargica are all being treated in one mental deficiency institution in each area. In London last year a hospital was established with a hundred beds for certified London cases under fifteen years under the Metropolitan Asylums Board.

In some cases patients are admitted at a much older age. The report of the Glasgow Public Health Department for March 1926 states that the Scottish Board of Health requested the Glasgow Parish Council to consider the question of providing accomodation for the treatment of 40 or 50 patients in the later stages of encephalitis lethargica and the Hospital Committee had agreed to give effect to this suggestion.

In the treatment of Parkinsonism hyoscine in some cases produces quite definite and even marked improvement. Mc Cowan Harris and Mann⁷⁰, experimenting with hyoscine in Parkinsonism to show its value as illustrated by its effect on the blood-sugar curve, found that this was made to approximate to the normal type, and are convinced that it is in the nature of a specific in the treatment of post-encephalitic Parkinsonism. After its administration a short period of drowsiness lasting for about two hours is often noticed and is followed by signs of physical and mental improvement. In some cases the beneficial results are more marked than in others, but in practically every case, given the correct dose, some improvement is obtained. It may be administered subcutaneously or by the mouth. Subcutaneously its action is more powerful and longer; starting with gr¹/₁₅₀ daily one may increase if necessary up to

gr ¹/₅₀ per diem. Orally larger doses are given three times a day after meals. If given before meals the dryness of the mouth and throat make mastication and deglutition difficult and unpleasant.

Recently Hall ⁴⁶ recommended large doses of tinct. Belladonna in the treatment of post-encephalitic Parkinsonism. Of 19 cases treated with belladonna in 6 there was no benefit, 3 stated they felt better, and in the other 10 there was definite improvement which was sometimes astonishing. One youth who was bed-ridden, had to be fed, and could not stand up without support, was brought to the Out-patients' Clinic in an ambulance from time to time. In October 1925 belladonna treatment was started and the next week he walked into the Clinic having come eighteen miles by train and tram! Hall reports other cases almost equally startling, but emphasizes the importance of big doses, η 30 to η 45 daily. Suggestion was excluded in all his cases. Belladonna relieves the hypertonus and allows the muscles to be used more freely, thus removing the effort required to perform any action. The resulting relief extends its beneficial influence to every part and so gives the patient a general feeling of well being. One of my cases is of interest in this connection.

Case 12, female, aet. 36, housewife. In April 1923 she had an attack of "influenza" during which she complained of diplopia and very severe headache. She was in bed about six weeks, having improved somewhat and then had a relapse. After this illness her friends noticed a distinct change in her character; she was quieter, instead of being a bright and cheerful girl she became dull and lazy. The headache persisted and she eventually had her eyes tested and glasses fitted for its relief which was successful to some extent. In August 1925 her mother noticed a stiffness and awkwardness in the way she walked and at this time she was always tired and took no interest in anything. Since the attack of "influenza" she has suffered from frequent "colds", and has been continually medically treated for her "stomach and nerves", the chief symptoms being anorexia, furred tongue, and the stiffness of gait and posture, with a lack of interest in anything and occasionally trembling of the limbs. These symptoms gradually became progressively worse. Examined in October 1925 she showed an increase of muscle tone of the extra-pyramidal type, diminution of muscular power, and a tendency to rhythmical tremor of all four limbs; increase of muscle tone of the neck; occasionally twitching of the right side of the face and neck, and a tendency to lean to the right. There

was no optic neuritis, Rombergism, or Babinski's sign; the superficial abdominal reflexes were brisk and equal and all other reflexes were normal. Speech was slow and monotonous. The mental state was normal. The tongue was coated with an unpleasant fawn-coloured fur. There was excessive salivation. The pulse was 108 and regular and the blood pressure 118-84. The heart was normal. There was slight dulness, with harsh breathing and prolongation of expiration, with occasional rhonchi at the apex of the right lung. There was well marked hypertonus of the abdominal muscles. The posture was typically Parkinsonian - mask-like face, head held stiffly erect, and hands carried in front of the body. The gait was ghost-like and floating, on the balls of the toes; the left heel could not be brought to the ground owing to the excessive tone of the gastrocnem-
-ious and soleus. From October 1925 to January 1926 the condition was practically stationary. She was confined to bed all day, only getting up for half an hour every morning to be washed and have the bed made. Her appetite was good and she complained of no headache, but of very persistent insomnia. She preferred to do without drugs for this as the medicinal tablets prescribed made her drowsy in the day time.

On January 31st 1926 she was put on tinct. belladonna in increasing doses until in a few days she was having η XXX three times a day. Owing to excessive mydriasis this had to be reduced to twice daily and this dose was continued with. On February 19th the condition was so much improved that she was going about the house all day, except for a short rest in bed in the afternoon. She was helping with the dusting of the rooms, and hoping to get out for a short walk on the first fine day although she had been confined to bed almost completely since October 1925. The muscular tone was still excessive, but much less than before, and though the Parkinsonian posture was still present in the gait and at rest, she could alk and perform actions very much more quickly and efficiently than a month previously; her tongue was clean and devoid of fur and she held her head in a much more comfortable looking position. This was all within three weeks of starting with the belladonna. In May 1926, still on the same dose of belladonna, she was getting out and about every day, coming to the surgery alone for her medicine, a walk of a quarter of a mile, and could go shopping errands alone quite well although still obviously Parkinsonian. She showed loss of convergence and weak ocular movements, held herself very stiffly erect and walked

very slowly, catalepsy and flexibilitas cerea were noted. In June 1926 she was still on belladonna ~~m. XXX~~ b.i.d. but the improvement had not lasted. She was very much thinner and weaker and could get out very little. Excessive salivation and constant dribbling was very troublesome. She took all morning to get washed and dressed even with assistance. In July she had become completely bedridden and had to be washed and fed. She was removed to the Infirmary where she became doubly incontinent and developed a large bed-sore. She was transferred to the work-house hospital and by August, the time of writing, the incontinence had disappeared and the bed-sore was healed, but she was still bed fast.

The experience of this case is what appears to be the general result. They usually improve for a time on belladonna, but there is a tendency for them to relapse again subsequently. Perhaps the best method is to give a mixture containing belladonna and either hyoscine or tinct. hyoscyamus.

General massage is of value in the treatment of Parkinsonism.

Meningeal cysts producing post-encephalitic Jacksonian epilepsy may be removed surgically; some have been cured in this way.

SUMMARY.

Encephalitis lethargica was first described by Economo in 1917. A few cases had been seen before that date. Since it was first recognised the disease has spread rapidly to all parts of the globe. It appears in epidemic form in the first quarter of the year and sporadic cases occur during the inter-epidemic periods. It attacks both sexes equally and may occur at any age from infancy to extreme old age, but the heaviest incidence falls on those approaching adult life. The case-mortality is probably a little over 25%.

Evidence of contagion is very rare but is sometimes seen. Two cases may occur in one house. In this connection I may mention that the young brother of my case 5 has for the past three months suffered from irregular jerking movements of the left arm, which causes him to drop things especially at meals, and a tendency to drag the right foot at times. On physical examination he appears to be normal in every respect. The symptoms are not sufficient to warrant a diagnosis of encephalitis lethargica but are very suggestive, occurring, as they do, in a house where a recognised case is living. Small pandemics have occurred in institutions. A mother suffering from the disease can infect her baby, and infection can also occur by placental transmission before birth.

Infectivity may persist for long periods, and lights up afresh as a recrudescence. The incubation period is about ten days but is probably variable and may be two weeks or more. The virus probably first infects the upper respiratory passages and passes on from there to the brain. Infection occurs from contact with a case of the disease or a "carrier". There is evidence that "carrier" infection occurs.

Pregnant women are not especially susceptible, nor is the disease more dangerous in them. Epidemic hiccough is probably a mild form of encephalitis lethargica.

The post-mortem findings are typical. Macroscopically there are signs of congestion of the brain and slight opacity of the meninges. Microscopically the lesions consist of an acute inflammation of the brain substance evidence by perivascular and parenchymatous small round cell infiltration, degeneration of neurones, and proliferation of neuroglia. Small perivascular haemorrhages are also seen. These changes may occur anywhere in the brain or spinal cord but affect especially the grey matter. The basal ganglia and the grey matter of the mid-brain and pons are the parts usually most involved.

Calcification in the vessel walls, and in the supporting tissues sometimes occurs in the anterior part of the globus pallidus. Oedema of the brain substance is sometimes marked.

"Minute bodies" have been observed within and without certain groups of nerve cells but their significance is not known. Certain experimenters claim to have transmitted the disease to rabbits and monkeys, and to have obtained a filterable virus from the brains of fatal cases and the naso-pharyngeal secretions of patients and healthy subjects capable of producing the disease in animals, but as these observations have not been confirmed by others it is premature to make any dogmatic statements on the nature or transmissibility of the causal organism except to say that it is a filterable virus.

The symptoms may be of almost any variety. The classification into types which has found most favour generally is on an anatomical basis and divides the disease into three main types - those with general symptoms, those with localising signs, and mild cases. The symptoms may also be divided into "positive" and "negative" according to whether they express exaltation or depression of function. Acute, subacute, and chronic cases occur.

The onset may be sudden, and its suddenness is sometimes dramatic resembling apoplexy, epilepsy, or syncope. In most cases, however, the onset is gradual and in many a prodromal period occurs. The prodromal period lasts from one to seven days but may be as long as three weeks. The most common prodromal symptoms are lethargy, headache, vertigo, and diplopia, but any symptom may be complained of. Case 1 was an ambulatory case with a definite prodromal period of about two weeks, during which headache, diplopia, and drowsiness were complained of. He then developed slight pyrexia and facial diplegia, and complained of excessive salivation. He was off work for about three weeks. Cases 4 and 9 also showed a prodromal period. In a number of cases no prodromal period can be observed and the onset may take various forms. Severe headache, malaise, neuralgic pains, vomiting and constipation are common early symptoms, while nocturnal excitement or involuntary muscular movements may be the first sign of the disease. The onset may simulate influenza or cerebral tumour very closely. Many cases have a very gradual onset with no history of fever and appear to be very chronic in type. Case 7 was of this nature.

The acute stage of the disease usually commences with pyrexia, although many cases are afebrile throughout. The temperature rises to 101°

or 102° , rarely higher, but hyper-pyrexia occurs occasionally and is usually fatal. Pyrexia usually lasts from two to five days, but may be as long as two weeks. The pulse is accelerated in relation to the temperature but may be rapid when the temperature is normal.

Headache is a specially common early symptom and is frequently unilateral. Vertigo is sometimes complained of and extreme general asthenia is often present. Vomiting after the prodromal period is very rare. Constipation is in most cases a very troublesome symptom and the tongue is usually very foul for a considerable period after the acute illness is past. In many cases a diffuse erythema appears during the pyrexial period and is usually very transient. In others the eruption may be purpuric, morbilliform, or scarlatiniform. A haemorrhagic syndrome occurs in some cases, evidenced by symptoms such as epistaxis, haematanesis, or purpuric eruptions. Disturbances of the liver occur frequently.

Many cases have a subacute pharyngitis which gives rise to no symptoms and has to be looked for. Bilateral parotitis occasionally develops during the acute stage, and sialorrhoea may occur early as in case 1. A simple catarrhal conjunctivitis may be the first symptom suggesting that the virus may gain entrance by the conjunctival route.

The most common symptom of the disease is lethargy. It is present in some degree in the majority of cases but in a certain number it is entirely absent. Case 2 was completely lethargic for three weeks and could only be wakened by shouting and shaking when he would complain of headache and diplopia. Case 3 lay like a log with immobile mask-like face. He was lethargic, but could easily be roused to answer questions, and mumbled his answers. Lethargy may be of any degree from slight drowsiness to profound coma. A lucid somnolence from which the patient can be easily roused is very common. Some degree of lethargy has been present in ten of the cases. Various causes for the lethargy have been put forward, but the one which appears the most probable is an extension of inflammation to the afferent paths interfering with stimuli to the thalamus.

Insomnia may be very intractable and may persist for a long period. Although sometimes associated with lethargy it frequently occurs without it. Nocturnal excitement is very common in children. Case 5 a boy of 19 had an apparent acute tonsillitis and five months later complained of somnolence and lassitude. Three months later he had another acute tonsillitis followed by nocturnal restlessness and insomnia lasting four months when he developed scarlet

fever. While pyrexial he slept soundly at night, but the insomnia returned when the temperature fell. Insomnia persisted for the next three months and then he had another acute tonsillitis, sleeping soundly while feverish once more. When seen five months later he was back at work, but still sleepless at night, only sleeping one night out of four. He also showed a change of character, being much more talkative and amiable, and he had developed an enormous appetite. An interesting point in this case is that pyrexia appeared to cure the insomnia, which suggests that the latter was due to some irritative lesion in the region of the thalamus. Two other cases had persistent insomnia, and in one of them it was the only symptom for nine months.

Delirium is a very prominent symptom in many cases and may be of any degree from muttering to maniacal. It usually only lasts about a week but may be much longer, and is as a rule worse at night frequently alternating with lethargy. In many cases the patient can easily be roused from his delirium to answer questions, and this lucidity is a very characteristic feature of the delirium. The delirium is frequently of the occupational type.

Early Parkinsonism is frequently present during the acute stage, often associated with lethargy. The mask-like face and the log-like immobility., the rigidity and the attitude of the arms are very characteristic, and may be accompanied by catalepsy and monotonous slurring speech.

Localising signs occur especially in the second type of the disease. Cranial nerve palsies are characteristically progressive, altering from day to day, and they are sometimes very transient. Frequently bilateral, one side is usually more affected than the other, and the two sides also differ as a rule in the time of onset and the duration of the paresis. Those supplying the ocular and facial muscles are most commonly affected, but any of the others, except possibly the first, may be involved in certain cases. Some cases show symptoms of cerebral irritation followed by paralysis indicating a cortical lesion, and quite a number of cases simulate cerebral haemorrhage. Case 4 complained of severe right frontal cephalgia. Drowsiness gradually developed a week later, and about a month after the first complaint he suddenly had an apparent apoplexy which left a complete right hemiplegia. This quickly improved but a similar seizure occurred a week later and the right side was again completely paralysed. He gradually sank and died seven weeks after the onset.

Localised nerve pains, some of which are probably of thalamic origin, are very common. Hemianaesthesia, hemianopia, and ataxia occur occasionally. Quite a large number of cases have signs of meningeal irritation and simulate cerebro-spinal fever. The spinal cord is sometimes involved, producing flaccid paralysis of the limbs and retention of urine. Peripheral neuritis is sometimes present.

Positive excito-motor phenomena first took a prominent place in the symptomatology of the disease in 1919, and they have now become features of common occurrence. Involuntary muscular movements are probably due to irritation of the lower motor neurones. Any muscle of the face, trunk, or limbs may be affected and tremor, twitchings, choreiform, myoclonic or shaking movements may occur. The myoclonic movements are rhythmical about 80 to 100 per minute and sometimes persist during sleep. Hiccough, which is a form of myoclonus, is not an uncommon symptom.

In rare cases myasthenia is simulated. In some cases polyuria develops, usually from the third to the seventh weeks; it often begins and ends quite suddenly. Pressure erythema or sloughing bed-sores may occur in spite of prophylactic measures.

A slight leucocytosis occurs in the blood during the acute stage, in rare cases a leucocytosis of 20,000 or 30,000 may be met with. The cerebro-spinal fluid shows characteristic changes. In the early stages it may be under increased pressure and is usually clear and colourless but may be blood tinged. There is a slight increase of cells which are practically all lymphocytes with a few plasma cells. The total protein shows a relatively small increase compared to the number of cells present. In the later stages the cerebro-spinal fluid is practically normal except for a small increase of chlorides, cells, and protein. A luetic curve with the Lange reaction occurs in about half the cases.

The diagnosis of such a disease as this is in many cases extremely difficult and sometimes can only be arrived at by a process of exclusion. Some types are characteristic and their diagnosis easy, one type of the disease usually predominates during any particular epidemic.

A careful detailed history of the onset and course is the most important diagnostic factor and skilled examination of the cerebro-spinal fluid is frequently of great assistance. Diagnosis depends on the recognition of an inflammation affecting larger or smaller areas of the brain and exclusion

of other inflammatory or toxic lesions. The more suggestive symptoms are diplopia, nystagmus, strabismus, lethargy, foul tongue, involuntary movements, and Parkinsonism. Case 6 was a mild case simulating influenza with transient diplopia and lethargy followed by complete recovery within a week.

Careful history taking and examination of the cerebro-spinal fluid, with other special factors in individual cases, serve to differentiate encephalitis lethargica from the long list of other diseases which may at one time or another be simulated. If the twelve cases under consideration are compared it will be found that, even in so small a number, the symptoms presented vary widely. Out of twelve cases there are eight distinct clinical types, and so dissimilar are these that they might all be entirely different diseases. This is a point which I wish to emphasize most especially as it is very prominently brought out by the cases under review. It is only by constantly keeping it in mind that one can possibly diagnose every case of encephalitis lethargica that presents itself for treatment and even then mistakes cannot be avoided. It is especially in the mild or abortive cases that difficulty arises, and in others it is only after observation for some months that the symptoms become definite enough to show its true nature.

The prognosis as regards life is always grave. A sudden onset simulating cerebral haemorrhage, a gradually deepening lethargy, or the occurrence of general symptoms without localising signs add to the gravity of the prognosis. Hyperkinetic cases are more virulent than amyostatic. In children early stupor with signs of meningeal irritation are of serious import.

The prognosis as regards complete recovery is equally important. Recrudescences occur frequently usually at epidemic periods, and two or more recrudescences are not uncommon. In a large number of cases residua appear after the acute illness is past. Residua may follow the mildest cases as well as the severe. In young children residua are more severe and in them a severe acute stage seems to favour the occurrence of residua.

The most common and serious residuum is Parkinsonism. It may follow an ambulatory attack of encephalitis lethargica. It usually develops six to twelve months after the acute stage, but the interval may be much longer. Complete recovery in the interval is rare, convalescence is usually protracted and the patient remains in poor health

and is easily tired and apathetic. Its development is frequently very gradual and in many cases it is not recognised for some time. Case 7 is a case of Parkinsonism following an ambulatory attack of encephalitis lethargica. She had nine months of severe nocturnal insomnia followed by eleven months during which her only complaints were weakness and lassitude. Signs of Parkinsonism affecting only the arms then appeared and the condition has so far remained stationary. She had had no acute illness for several years previous to the onset of insomnia.

A slight injury sometimes precipitates the onset of Parkinsonism. This is of importance from the point of view of compensation. Case 8 is a man with Parkinsonism following an acute encephalitis lethargica resembling epidemic influenza. The face and right arm are especially affected but the left arm and both legs slightly also. He has had three attacks of "influenza" since the first one and these are probably recrudescences. He has become much more talkative and cheerful since his illness began.

The prognosis of Parkinsonism is very uncertain. Some cases progress rapidly and end fatally in six months or a year. Others progress until they are helpless and bed-ridden and then remain stationary, while many continue to get about

for years. Case 9 was one of the first cases to occur in England. His primary attack was in March 1918, and his Parkinsonism has remained stationary for at least six years. He is unable to work, but can get about as well as anybody. Some cases gradually improve and recover apparently completely. Periods of improvement to a surprising extent are not uncommon. The age of the patient, the absence of the pill-rolling tremor of the hands, the early appearance of rigidity, and the presence of other residua serve to distinguish Parkinsonism from paralysis agitans.

Excito-motor residua, not infrequently associated with Parkinsonism, occur in some cases. The movements are involuntary, rhythmical, and of various kinds. They may be choreic, myoclonic, bradykinetic, or shaking in character and may affect any muscle in the body. The muscles most commonly affected are those of the limbs, the abdominal wall, the diaphragm, and the larynx. The movements usually gradually improve but often last for years.

Mental residua occur very frequently especially in children and young adults. The deficiency may be only slight or it may amount to idiocy. Some cases have symptoms of nervous exhaustion such as lack of energy, depression, and

insomnia. Moral changes such as lying, theft, and changes of character are common. Some of these children become normal again after a time. The moral changes frequently take the form of the badly behaved child and in these, early discipline and strict lessons in obedience may do much good, but it must be remembered that probably the child was originally a good child and the change is due to disease of the brain which no discipline will remove. Quite a number of these cases have been charged in the police courts with theft and immoral conduct, and this leads to a very important medico-legal problem. They cannot of course be said to be responsible for their actions.

In children nocturnal restlessness and excitement is a frequent residuum; it appears in convalescence and after lasting some months it gradually passes off. Along with it there is usually some drowsiness in the day time but a few cases sleep all day. Cases 10 and 11 are two boys aged eight and nine whose illnesses commenced with nocturnal excitement. In case 10 this lasted about six months and he slept all day. This was followed a year later by retropulsion. During the next four months a spastic hemiparesis of the left side gradually developed and was accompanied by severe retropulsion,

and he showed a marked change in character, always spitting and swearing. He had been in good health for at least two years before the onset of these symptoms. In case 11 the nocturnal excitement only lasted about four months and was accompanied by propulsion. Three months later he developed a spastic paresis of the right arm and of both legs which was accompanied by retropulsion. The similarity of these two cases is striking and they constitute a clinical type.

Respiratory residua of various kinds frequently occur. The commonest is tachypnoea, and involuntary muscular movements sometimes synchronise with the respirations. Residual paralyses occur occasionally, usually a spastic hemiplegia or diplegia and ataxia and incoordination of the arms not infrequently accompany it as in cases 9, 10 and 11. Any form of ophthalmoplegia may be left as a residuum, and severe optic neuritis sometimes occurs late in the disease. Attacks of drowsiness and headache sometimes recur from time to time after the acute illness is past. The occurrence of trophic residua such as marked obesity are of interest as they suggest hypophyseal disorder.

The morbid anatomy of these residua is considered to be a hyaline and calcareous degeneration. of the vessel walls involving the adventitia and the media, interfering with the blood supply to the nervous elements and leading to a gradual loss of functional activity. In cases of Parkinsonism these changes involve especially the basal ganglia but changes have also been found in the cells of the substantia nigra in some cases. Mental residua and involuntary movements are probably due to lesions of the cortex and cord respectively, while metabolic disturbances point to inflammation of the controlling brain centres.

Investigation into the morbid anatomy of encephalitis lethargica has thrown much light on the histology of certain neuroses and psychoses which were believed to be of psychic origin.

The treatment of encephalitis lethargica involves the duties of the medical attendant and the Medical Officer of Health both to the public and to the patient. In the interests of public health all possible means should be taken to investigate the epidemiology and prevent the spread of the disease. Wherever possible cases should be treated in hospital. ^WWhen treated at home isolation is essential and the general principles for any infectious disease should be followed. Children in the affected house should

be kept from school for three weeks, and members of the household should be examined from time to time for evidence of the disease.

The patient must be confined to bed, however slight the attack, and as good nursing is the most important factor in treatment a trained nurse should be in attendance. The treatment is largely symptomatic with antiseptic cleansing of the mouth and throat and prevention of bed-sores, while pulmonary and cystic complications should be watched for. Lumbar puncture is beneficial in some cases.

The drug that has been most largely used is hexamine, but as it is liable to damage the kidneys it should not be given in large doses over a long period, and the urine should be examined daily during its exhibition. There is no definite proof that it is of any value. Improvement has followed its administration intravenously. Other drugs that have been recommended include strychnine, quinine, sodium salicylate, potassium bromide, potassium iodide, luminal, and good results have been obtained in some cases by large doses of intravenous iodine. Intrathecal injections of convalescents' serum, and the production of a fixation abscess have also been tried with some success. Massage, hot baths, and electrical treatment are useful in convalescence.

In cases in the later stages institutional treatment is often necessary. Some cases can be certified while others require institutional treatment just as much. In certain areas hospitals have been established for the treatment of these cases only, and this movement is spreading.

In the treatment of Parkinsonism hyoscine or belladonna, and general massage have been found most successful. Hyoscine or belladonna may be given by the mouth but the drug has to be continued indefinitely. Marked improvement occurs in some cases but does not last, the drug appears to lose its effect after a time. Case 12 had an attack of encephalitis lethargica resembling "influenza" with incomplete recovery, and Parkinsonism developed two and a half years later. She had been confined to bed for three months when belladonna treatment was started, and within a month she was going out for a walk every day. The improvement unfortunately only lasted four months and in five months she was completely helpless and confined to bed once more. This is the general experience of belladonna treatment.

Surgical treatment for the removal of localised meningeal cysts causing Jacksonian epilepsy has cured residua in some cases.

CONCLUSIONS.

1. Encephalitis lethargica is an epidemic disease of the central nervous system quite distinct from similar affections such as acute poliomyelitis and cerebro-spinal fever.
2. Since its first appearance there has been a rapid increase in the number of cases, and this increase still continues.
3. The causal organism has not yet been isolated but it is of the nature of a filterable virus.
4. Many cases are very gradual in onset and of a chronic nature throughout, and in these the acute stage is either absent or is so mild as to pass unnoticed even by the patient.
5. There has been a very marked change in type, the initial "negative" phase in which lethargy and palsies predominated being replaced by a "positive" phase with insomnia and involuntary movements as prominent symptoms and lethargy slight or absent.
6. The symptoms vary widely in different cases and many are liable to be missed unless a careful lookout is kept for the disease.

7. No drug has yet been discovered which has any permanent effect on the course of the disease.

8. The prognosis of Parkinsonism is very uncertain but it may remain practically stationary for at least seven years.

9. In some cases of Parkinsonism great improvement follows the use of hyoscine or belladonna, but this improvement is only temporary and the drug loses its power after a time.

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